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VOLUME 98(11) — NOVEMBER 1989

ANNALS

OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

ANNALS OF HEAD & NECK MEDICINE & SURGERY

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MORTALITY AFTER NASOPHARYNGEAL RADIUM IRRADIATION FOR EUSTACHIAN TUBE DYSFUNCTION

ADENOID CYSTIC CARCINOMA OF THE PAROTID GLAND

OSTEOMYELITIS OF THE FRONTAL BONE

TREATMENT OF DEPRESSED TINNITUS PATIENTS WITH NORTRIPTYLINE

ASALOID-SQUAMOUS CARCINOMAS OF THE UPPER AERODIGESTIVE TRACTS

TOTAL CERVICAL TRACHEAL STENOSIS: TREATMENT BY LASER, DILATION, AND STENTING

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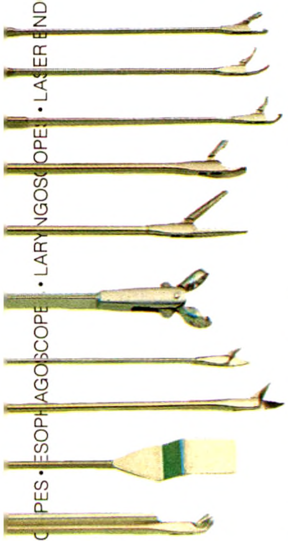

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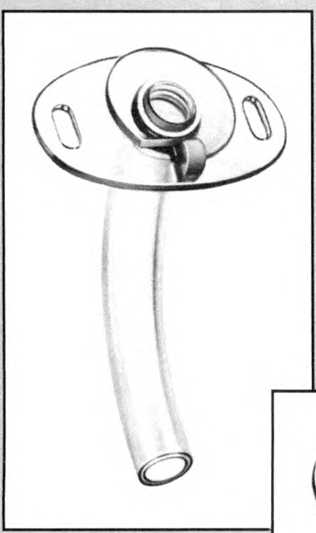

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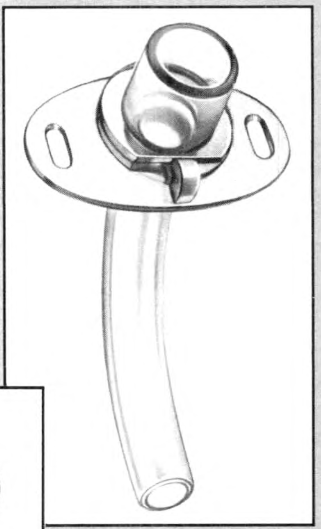

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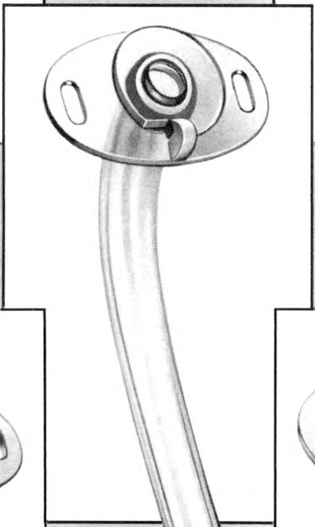

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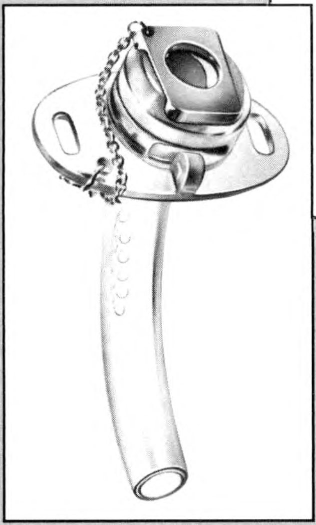

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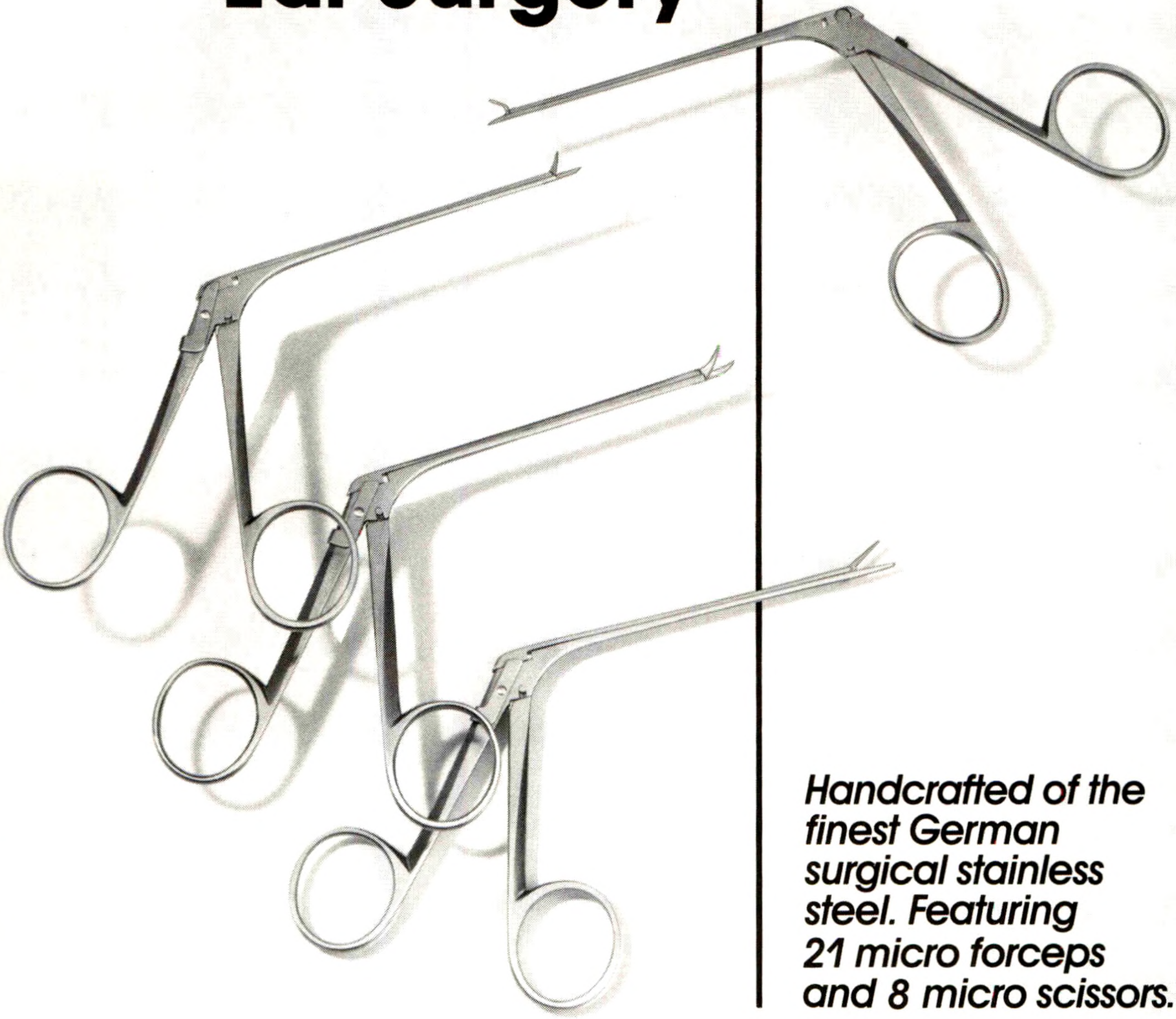

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MORTALITY AFTER NASOPHARYNGEAL RADIUM IRRADIATION FOR EUSTACHIAN TUBE DYSFUNCTION

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Cause-specific mortality of 2,510 persons treated before 1965 by nasopharyngeal radium irradiation (average exposure, 1,200 mg/min), followed to 1985, was compared to that of 2,199 nonexposed comparison subjects. No excess was found for the exposed group in overall mortality, cancer mortality, or in mortality of cancer of specific sites. A marginal excess ($p = .07$) of malignancies of the lymphatic and hematopoietic system was noted in exposed males only. Only one brain cancer (0.2 per 10^4 person-years) was identified in the exposed group, and two (10.3 per 10^4 person-years) in the nonexposed group.

KEY WORDS — breast neoplasms, epidemiology, head and neck neoplasms, leukemia, mortality, radiation carcinogenesis, radium irradiation.

INTRODUCTION

Nasopharyngeal irradiation by application of radium 226 was introduced by Crowe and Baylor in 1924 and reported in 1939.[1] This therapy was designed to improve the function of the eustachian tube by shrinking lymphoid tissue in and around the tubal orifice. It has appeared to be effective in children suffering from secretory otitis media[2] and in airmen suffering from barotrauma.[3]

Nasopharyngeal radium irradiation became routine medical practice in the United States and Europe in the 1940s and 1950s. Consideration of the potential hazards for cancer from radiation treatment[4] and the availability of alternatives[5] made the therapy practically obsolete.

Two smaller studies[6,7] from the United States have evaluated the subsequent risk for cancer among children treated for various conditions by nasopharyngeal application of radium 226. Because of the interest in studies of cancer in subjects exposed to low dose irradiation, we undertook the current study, which assesses the risk for cancer mortality among a larger series, mostly of children, treated by nasopharyngeal irradiation with radium 226 in the Netherlands.

MATERIALS AND METHODS

Study Population. By a systematic review of the medical records in five otolaryngology clinics in the Netherlands, 2,542 persons born after 1909 and treated with nasopharyngeal radium irradiation in the years 1945 to 1965 were identified and included for study as the exposed group. The great majority of the included patients (92.9%) had been treated for secretory otitis media (60.5%) and recurrent otitis (32.4%).

After the radium-exposed group had been assembled from the clinic records, a group of nonexposed subjects was selected from the same clinic records in a random fashion until equal numbers of nonexposed and exposed subjects were included for each clinic, stratified for sex, year of birth (5-year age groups), and year of first contact (5-year time periods). The nonexposed subjects had been treated without the use of radium for a variety of head and neck disorders, including hypertrophic tonsils and adenoids (41.1%), recurrent otitis (28.2%), rhinosinusitis (6.7%), secretory otitis media (5.2%), and perceptive deafness (1.4%). In total, 2,381 nonexposed subjects were identified and included for study.

When sex was not specified in the available records, it consequently was defined on the basis of first names only. Names for which gender could not be specified were recorded as sex unknown. By an oversight, for these exposed persons of unknown sex, no controls were selected. This explains the difference in size of the two study groups. In the course of the follow-up, the sex of all exposed persons was determined.

Excluding exposed subjects for whom the date of first treatment was unknown and nonexposed subjects for whom the date of first treatment was either unknown or prior to the period of radium use in the

---

From the Department of Otolaryngology, Hospital of Sittard, Sittard, the Netherlands (Verduijn); and the Department of Public Health and Social Medicine, Erasmus University, Rotterdam, the Netherlands (Hayes, Looman, Habbema, van der Maas). This work was supported by grants from the Ministry of Education and Sciences of the Netherlands and the Netherlands Cancer Foundation.

REPRINTS — Peter G. Verduijn, MD, Dept of Otolaryngology, Hospital of Sittard, Walramstraat 23, 6131 BK Sittard, the Netherlands.

TABLE 1. NUMBER OF STUDY SUBJECTS BY CLINIC, SEX, AND EXPOSURE TO RADIUM

	Males		*Females*		*Total*	
Clinic	*Exposed*	*Nonexposed*	*Exposed*	*Nonexposed*	*Exposed*	*Nonexposed*
1	704	645	468	463	1,172	1,108
2	188	158	140	122	328	280
3	388	334	346	284	734	618
4	81	77	59	53	140	130
5	87	43	49	20	136	63
Total	1,448	1,257	1,062	942	2,510	2,199

respective clinics, 2,510 (99%) exposed and 2,199 (92%) nonexposed persons remained for study. All statistics in this paper concern these selected populations. Table 1 shows the number of exposed and nonexposed subjects by clinic.

In Table 2 the numbers of exposed and nonexposed subjects are presented by age at first contact, sex, and year of first contact for all five clinics combined. Overall, the numbers of exposed and nonexposed subjects are well balanced with respect to age and sex.

Follow-up. The cohort was followed up from the time of first contact until death, emigration, or, for those still alive and resident in the Netherlands, Feb 1, 1985. Tracing efforts were carried out by various means, including search of municipal registries, state registries, conscription files, and telephone books. For those who could not be traced, a separate search was made in the death registry files of the Central Bureau of Genealogy. A summary of the follow-up is presented in Table 3. In total, 94.0% of the study persons could be located, 91.1% alive and 2.9% deceased. Among the 6.0% not located, 3.8% were known to have emigrated and 2.2% could not be traced.

For the deceased, cause-of-death information was requested from the Chief Inspector of Public Health. Of the 138 persons known to have died, the underlying cause of death was determined for 133 (96%). The cause of death could not be determined for four subjects because they had died outside the country, and for one subject because the death certificate could not be found.

Dosimetry. Radiation therapy was conducted by introducing a radium sulfate–containing cylinder via the nostril and leaving it for some minutes close to the orifice of the eustachian tube in a manner similar to that described by Crowe and Baylor.[1] Type of applicator (milligrams of radium) and number and times of applications differed in each of the five clinics included in this study. However, for every irradiated individual, these parameters were known (Table 4). The largest number of persons (n = 1,172) were irradiated with an applicator containing 25 mg radium sulfate in a nickel-alloy capsule (Monel metal) in four sessions of 7 minutes for subjects under 16 years of age and for 15 minutes for subjects over 16 years of age.

Distance between the radiating source and the tissues of the head and neck region is a function of the size of the individual at the time of treatment and the exact positioning of the applicator. Estimations of dose were made for selected tissues for "average persons" in each age group, on the basis of measurements taken from plain films of 25 individuals between the ages of 3 and 16 years and on isodose curves for the employed applicators.

The dosage (in centigrays per hour) for the thyroid, parotid, and pituitary glands was estimated for the applicators used in the five clinics. The absorbed tissue doses ranged, depending on clinic and age, for the thyroid from 2 to 7 cGy, for the parotid gland from 4 to 19 cGy, and for the pituitary gland from 10 to 36 cGy. The doses estimated to be absorbed by the adjacent tissues of the orifice of the eustachian tube and the nasopharyngeal mucosa are considerably more (Table 4).

Methods of Analysis. The mortality rates per 10,000 person-years for exposed and nonexposed subjects were compared by cause of death for males and females.[8,9] The start of the follow-up period for treated persons was taken to be the date of first ir-

TABLE 2. NUMBER OF EXPOSED AND NONEXPOSED INDIVIDUALS BY YEAR AND AGE AT FIRST CONTACT AND SEX

		Age at First Contact (yr)											
		0-5		*6-10*		*11-15*		*16-25*		*26-75*		*Total*	
Year of First Contact	*Sex*	*Exp*	*NExp*	*Exp*	*NExp*	*Exp*	*NExp*	*Exp*	*NExp*	*Exp*	*NExp*	*Exp*	*NExp*
1935-1950	M	92	41	40	17	13	8	18	5	9	2	172	73
	F	96	36	35	11	12	4	15	6	7	4	165	61
1951-1955	M	224	209	84	84	29	22	26	34	39	26	402	375
	F	174	163	73	84	33	26	20	26	17	15	317	314
1956-1960	M	278	244	104	95	36	35	6	18	29	28	453	420
	F	209	186	73	64	29	29	11	13	11	13	333	305
1961-1965	M	191	184	99	102	22	41	15	18	37	38	364	383
	F	107	125	65	72	28	36	4	10	15	17	219	260
Total	M	785	678	327	298	100	106	65	75	114	94	1,391	1,251
	F	586	510	246	231	102	95	50	55	50	49	1,034	940

Age or year of first contact is missing for 85 exposed persons and eight nonexposed persons.

Exp — exposed, NExp — nonexposed.

TABLE 3. FOLLOW-UP STATUS OF STUDY POPULATION AS OF FEBRUARY 1, 1985

	Exposed		*Nonexposed*		*Total*	
Status	*n*	*%*	*n*	*%*	*n*	*%*
Located	2,360	94.0	2,066	94.0	4,426	94.0
Alive	2,287	91.1	2,001	91.0	4,288	91.1
Deceased	73	2.9	65	3.0	138	2.9
Not located	150	6.0	133	6.0	283	6.0
Emigrated	95	3.9	84	3.8	179	3.8
Lost	55	2.1	49	2.2	104	2.2
Total	2,510	100.0	2,199	100.0	4,709	100.0

radiation; for untreated persons the date of first consult was used. The end of the period of follow-up for all cases was the date of death, emigration, or loss to follow-up or Feb 1, 1985.

Assuming that the number of cases is distributed as a Poisson variable, we used an exact procedure for testing the null hypothesis for the relative risk and for the calculation of 95% confidence intervals.[10]

RESULTS

As shown in Table 5, the all-causes mortality for both sexes combined was similar in the exposed group (11.5 deaths/10^4 person-years) and the nonexposed group (11 deaths/10^4 person-years). For males, the rate in the exposed group (15.4 deaths/10^4 person-years) is slightly higher than the rate in the nonexposed group (13.1 deaths/10^4 person-years), while for females the rate in the exposed group (6.3 deaths/10^4 person-years) is about 75% of the rate in the nonexposed group (8.3 deaths/10^4 person-years).

For causes of death other than cancer, there are no remarkable differences between exposed and nonexposed groups. For cancer at all sites, in males there was a nearly threefold excess in the exposed group (relative risk, 2.78), while for exposed females the rate was about half that of the nonexposed group (relative risk, 0.56). Neither of these findings was, however, statistically significant.

In Table 6, the results by specific cancer site are shown. The number of cases for any one site is small, limiting the conclusions that can be drawn. Four cases of lymphatic and hematopoietic tumors were identified in radium-exposed males, while none were found in the nonexposed group (Fisher's exact test, $p = .07$). The two deaths of leukemia occurred in the exposed group 20 and 24 years after treatment (Table 7). In females the small number of cancer deaths in the exposed group did not appear to be concentrated in particular sites. There were smaller numbers of brain and breast cancers and of the lymphatic and hematopoietic malignancies among exposed females. Only one death due to brain cancer of an unspecified nature was identified in the exposed group, while two were found in the nonexposed group. None of the differences was statistically significant.

DISCUSSION

Irradiation of the head for the treatment of tinea capitis has been associated with an excess risk for leukemia[11,12] consistent with findings after exposure to larger proportions of body marrow, such as following radiotherapy of the spine for ankylosing spondylitis in adults and of the chest in children.[13] Also, excess risk for tumors of the CNS has been found in children treated for tinea capitis,[11,12] and for meningiomas among subjects frequently exposed to full-mouth dental x-ray series.[14] The risks for leukemia and CNS cancer found in these studies were associated with exposures of about 30 and 150 cGy to the respective target organs. The risks were generally 2- to 3.5-fold greater than expected, although in the study of Ron et al[12] the excess for leukemia reached only marginal levels of statistical significance.

During nasopharyngeal radium therapy, adjacent tissues receive very high exposures to beta and gamma radiation. Tissues more distant than 1 cm from the source are only exposed to gamma radiation, which falls off rapidly inversely with the square of the distance (Table 4).[15]

Two prior studies of subjects treated by radium applicators for head and neck conditions have been carried out. Hazen et al[6] followed up, for an average of 14.6 years, 417 children treated with a 25-mg radium applicator (usual dosage per treatment, 300 to 600 mg/min) and compared the subsequent occurrence of cancer to that of 2,746 siblings. Only two malignant and five benign neoplasms were identified in the exposed group, compared to ten

TABLE 4. RADIATION METHODS AND DOSES TO DIFFERENT ANATOMIC SITES FOR EACH OF FIVE PARTICIPATING CLINICS

		Treatment Parameters			*Estimated Radiation Dose (cGy)*			
Clinic	*No. of Patients*	*mg Ra*	*Time (min)**	*Sessions*	*Thyroid*	*Parotid*	*Hypophysis*	*Adjacent Tissue*
1	1,172	25	28- 60	4	2-3	6- 8	12-14	4,480- 9,600
2	328	50	36- 72	3	5-7	14-19	29-36	11,520-23,040
3	734	25	40- 80	4	3-4	8-11	16-20	6,400-12,800
4	140	10	60-240	1-4	2-3	4-13	11-18	3,555-14,220
5	136	25	26- 52	3	2-3	5- 7	10-13	4,160- 8,320

Ra — radium.

*Total exposure time, age-dependent.

TABLE 5. NUMBER OF DEATHS, CUMULATIVE MORTALITY RATE (PER 10,000 PERSON-YEARS, 1945-1985) FOR EXPOSED AND NONEXPOSED SUBJECTS, AND RELATIVE RISKS AND CONFIDENCE INTERVALS ASSOCIATED WITH EXPOSURE, BY SEX

	Male						*Female*						*Total*					
	Exposed		*Non-exposed*				*Exposed*		*Non-exposed*				*Exposed*		*Non-exposed*			
Cause of Death	*n*	*Rate*	*n*	*Rate*	*RR*	*95% CI*	*n*	*Rate*	*n*	*Rate*	*RR*	*95% CI*	*n*	*Rate*	*n*	*Rate*	*RR*	*95% CI*
Total (all causes)	56	15.4	44	13.1	1.18	(.77-1.80)	17	6.3	21	8.3	0.75	(.37-1.52)	73	11.5	65	11.0	1.04	(.73-1.51)
Cancer	15	4.1	5	1.5	2.78	(.96-9.36)	6	2.2	10	4.0	0.56	(.17-1.69)	21	3.3	15	2.5	1.30	(.64-2.71)
Cardio-vascular	12	3.3	15	4.5	0.74	(.32-1.72)	4	1.5	3	1.2	1.24	(.22-8.38)	16	2.5	18	3.1	0.82	(.19-1.72)
Accidents/suicide	17	4.7	15	4.5	1.05	(.49-2.21)	3	1.1	2	0.8	1.40	(.16-17.7)	20	3.2	17	2.9	1.09	(.55-2.22)
Other	9	2.5	7	2.1	1.19	(.40-3.70)	4	1.5	6	2.4	0.62	(.13-2.65)	13	2.0	13	2.2	0.93	(.40-2.17)
Unknown	3	0.8	2	0.6	1.39	(.16-17.6)	0	—	0	—	*	*	3	0.5	2	0.3	1.39	(.16-17.6)
No. in group	1,448		1,257				1,062		942				2,510		2,199			
Person-years	36,387		33,680				27,048		25,202				63,435		58,882			

n — number of deaths, RR — relative risks, 95% CI — confidence intervals.

*Impossible value (not defined).

and 23, respectively, in the siblings. No excess risk was found in this small study group.

More recently, Sandler et al[7] followed up, for 18 to 35 years, 904 persons treated with a 50-mg radium applicator (usual dosage, 4,208 mg/min) and compared the subsequent cancer occurrence to that of 2,021 nonexposed persons. Three brain tumors and an anaplastic cancer of the soft palate were identified in the exposed group, while no cancers of the head and neck were found in the nonexposed group ($p < .05$). No other excesses in cancer risk were found.

The present study was similar in design to that of Sandler et al. The study group was, however, considerably larger (2,510 exposed, 2,199 nonexposed), and the average dosage lower (average, 1,198 mg/min). In the Netherlands, unilateral treatment had been the standard, whereas bilateral treatment had been used on subjects studied by Sandler et al.[16]

We calculated, for each exposed person in the study group, the probability of being alive at the end of the study period, using age-, sex-, and period-specific death rates for the Netherlands.[17] The expected number of deaths was very close to the number of 56 male and 17 female deceased subjects identified among the exposed in this study. The overall death rate in the study group is comparable to the death rate in the Dutch population as a whole.

In the present study no overall significant excesses were found for cancer mortality. When examined by sex, there were no notable differences in mortality between exposed and nonexposed subjects due to all causes or due to noncancer causes of death. For cancer, a marginal ($p = .07$) excess was noted for lymphatic and hematopoietic malignancies, in males only. The small numbers, the inconsistency over the sex groups, and the observation that the latency period (Table 7) is much longer than that often observed for radiation-associated malignancies of the lymphatic and hematopoietic system are not supportive of a causal association. We found no evidence for an excess of brain cancer in this group.

TABLE 6. NUMBER OF CANCER DEATHS, CUMULATIVE CANCER MORTALITY RATE (PER 10,000 PERSON-YEARS, 1945-1985) FOR EXPOSED AND NONEXPOSED SUBJECTS, AND RELATIVE RISKS AND CONFIDENCE INTERVALS ASSOCIATED WITH EXPOSURE, BY SEX

	Male						*Female*						*Total*					
	Exposed		*Non-exposed*				*Exposed*		*Non-exposed*				*Exposed*		*Non-exposed*			
Cancer Site	*n*	*Rate*	*n*	*Rate*	*RR*	*95% CI*	*n*	*Rate*	*n*	*Rate*	*RR*	*95% CI*	*n*	*Rate*	*n*	*Rate*	*RR*	*95% CI*
Total (all sites)	15	4.1	5	1.5	2.78	(.96-9.36)	6	2.2	10	4.0	0.56	(.17-1.69)	21	3.3	15	2.5	1.30	(.64-2.71)
Brain	1	0.3	0	—	*	*	0	—	2	0.8	0	(0-4.96)	1	0.2	2	0.3	0.46	(.01-8.73)
Head and neck	0	—	0	—	*	*	0	—	0	—	*	*	0	—	0	—	*	*
L/H	4	1.1	0	—	*	(.61-*)	1	0.4	2	0.8	0.47	(.01-8.77)	5	0.8	2	0.3	2.32	(.38-23.5)
Breast	0	—	0	—	*	*	0	—	2	0.8	0	(0-4.96)	0	—	2	0.3	0	(0-4.94)
Other	10	2.7	5	1.5	1.86	(.58-7.12)	5	1.8	4	1.6	1.16	(.25-5.72)	15	2.4	9	1.5	1.55	(.63-4.09)
No. in group	1,448		1,257				1,062		942				2,510		2,199			
Person-years	36,387		33,680				27,048		25,202				63,435		58,882			

n — number of cancer deaths, RR — relative risks, 95% CI — confidence intervals, L/H — lymphatic and hematopoietic system.

*Impossible value (not defined or infinitely high).

TABLE 7. INDIVIDUAL DATA OF DEATHS DUE TO TUMORS OF LYMPHATIC AND HEMATOPOIETIC SYSTEM AND BRAIN FOR RADIUM-EXPOSED AND NONEXPOSED PERSONS, BY SEX

Sex	*Group*	*Tumor Site*	*ICD9**	*Diagnosis*	*Year of Birth*	*Dose (cGy)*	*Year of I/C*	*Year of Death*
Male	Exposed	L/H	202.8	Malignant lymphoma	1953	700	1963	1980
			205.1	Chronic myeloid leukemia	1934	1,500	1956	1976
			205.0	Acute myeloid leukemia	1947	750	1953	1977
			202.1	Mycosis fungoides	1917	1,200	1954	1963
		Brain	239.6	Nonspecified brain tumor	1913	1,500	1962	1971
	Nonexposed	L/H						
		Brain						
Female	Exposed	L/H	205.1	Chronic myeloid leukemia	1943	1,500	1955	1983
		Brain						
	Nonexposed	L/H	205.0	Acute myeloid leukemia	1947		1951	1978
			206.0	Acute monocytic leukemia	1915		1962	1980
		Brain	191.6	Malignant tumor of cerebellum	1958		1959	1982
			191.9	Malignant brain tumor	1950		1953	1981

I/C — irradiation or first contact, L/H — lymphatic and hematopoietic system.

*International Classification of Diseases, 9th revision, clinical modification, 1978 Commission on Professional and Hospital Activities.

The observation of some excess in cancer for exposed males, and some deficit for exposed females, does not lead to a ready interpretation. We are continuing our follow-up efforts to ascertain cases of patients who have not died, which may clarify our results.

We found no deaths due to breast cancer in the exposed group, and two cases in the nonexposed group. Hazen et al[6] found no cases in their exposed series, and three in the siblings, while Sandler et al[7] found no cases in the exposed group and five in the siblings. Sandler et al[7] pointed out the possibility of decreased incidence of breast cancer in their series being related to alterations in pituitary function due to nasopharyngeal radium treatments. Our findings are consistent with that suggestion.

In summary, the present study has found no excess of cancer mortality at any site associated with radium exposure by the Crowe and Baylor[1] therapy. Specifically, the finding of Sandler et al[7] of an excess of head and neck cancer was not found in this study group. That average exposures were lower in the Netherlands may have contributed to this finding. Also, the small number of cases, even in our relatively large study group, makes precise comparisons between studies difficult.

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REFERENCES

1. Crowe SJ, Baylor JW. The prevention of deafness. J Am Med Assoc 1939;112:585-90.

2. Bordley JE, Hardy WG. The efficacy of nasopharyngeal irradiation for the prevention of deafness in children. Acta Otolaryngol [Suppl] (Stockh) 1955(suppl 120).

3. Fowler EP Jr. Irradiation of the eustachian tube. An anatomic, physical, and clinical study of a treatment for recurrent otitis media applied to aero-otitis. Arch Otolaryngol 1946; 43:1-11.

4. Robbins LL, Schulz MD. Potential hazards from radiation treatment of hypertrophied lymphoid tissue in the nasopharynx. Laryngoscope 1949;59:147-55.

5. Armstrong BW. A new treatment for chronic secretory otitis media. Arch Otolaryngol 1954;59:653-4.

6. Hazen RW, Pifer JW, Toyooka ET, Livingood J, Hempelmann LH. Neoplasms following irradiation of the head. Cancer Res 1966;26:305-11.

7. Sandler DP, Comstock GW, Matanoski GM. Neoplasms following childhood radium irradiation of the nasopharynx. J Natl Cancer Inst 1982;68:3-8.

8. Fleiss JL. Statistical methods for rates and proportions. New York: John Wiley, 1981.

9. Rothman KJ, Boice JD. Epidemiologic analysis with a programmable calculator. Bethesda, Md: Public Health Service, National Institutes of Health, 1979.

10. Mulder PGH. The relative risk in a cohort study with Poisson cases. Comput Methods Programs Biomed (in press).

11. Shore RE, Albert RE, Pasternack BS. Follow-up study of patients treated by x-ray epilation for tinea capitis: resurvey of post-treatment illness and mortality experience. Arch Environ Health 1976;31:21-8.

12. Ron E, Modan B, Boice JD Jr. Mortality following radiotherapy for ringworm of the scalp. Am J Epidemiol 1988;127: 713-25.

13. Boice JD Jr, Land CE. Ionizing radiation. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer epidemiology and prevention. Philadelphia: WB Saunders, 1982:231-53.

14. Preston-Martin S, Yu MC, Henderson BE, Roberts C. Risk factors for meningiomas in men in Los Angeles County. JNCI 1983;70:863-6.

15. Garsou J, Boniver R. A propos de la repartition du debit de dose absorbee autour de la sonde de Crowe. J Belge Radiol 1971;54:701-8.

16. Sandler DP, Matanoski G, Comstock GW, Mitchell T. Health consequences of nasopharyngeal radium exposure. In:

Symposium on biological effects, imaging techniques and dosimetry of ionizing radiation. US Department of Health and Human Services, Public Health Service, Food and Drug Administration, Bureau of Radiological Health, Rockville, Md: HHS Publ (FDA) 80-8126, 1980:15-24.

17. Sterftetafels voor Nederland, afgeleid uit waarnemingen over de periode 1950-1952, Centraal Bureau voor de Statistiek, Voorburg, 1954.

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ADENOID CYSTIC CARCINOMA OF THE PAROTID GLAND: A REVIEW OF SURGICAL MANAGEMENT WITH REFERENCE TO THE FACIAL NERVE

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The purpose of this study was to review a large series of patients with adenoid cystic carcinoma of the parotid gland in order to develop clinical criteria for sacrifice versus selective sparing of the seventh nerve. We studied 43 patients followed over 36 years. Study patients were grouped according to the preoperative status and intraoperative management of the facial nerve. Criteria for choosing various management strategies are discussed.

KEY WORDS — adenoid cystic carcinoma, facial nerve, parotid gland.

INTRODUCTION

The malignancy of adenoid cystic carcinoma is recognized widely today, but was questioned as recently as 20 years ago.[1] The earliest treatment consisted of local excision. As the course of this lesion became better understood, it seemed likely that more extensive surgery might improve the chances of survival. The proximity of the tumor to the facial nerve, the propensity for perineural invasion, and the poor prognosis associated with nerve involvement make decisions regarding the surgical management of the facial nerve of central importance. A review of the literature in 1977 reported strong opinions both for and against sacrifice of the facial nerve.[2] These studies, however, were anecdotal. Larger populations studied over longer periods support sparing the facial nerve in carefully selected cases.[3,4] Our review of 43 cases treated over 36 years focuses on the conditions under which the facial nerve may be preserved relatively safely in surgical therapy of adenoid cystic carcinoma of the parotid gland.

MATERIALS AND METHODS

Forty-three patients with adenoid cystic carcinoma of the parotid gland treated by the senior author (J.J.C.) between 1949 and 1984 were studied. Five-year follow-up data were available for 36 patients. About half the patients (52%) underwent completion surgical extirpation shortly after receiving preliminary surgical therapy elsewhere.

This study assessed management of adenoid cystic carcinoma of the parotid gland with special reference to the facial nerve. Operative planning in this series dictated facial nerve sacrifice if any preoperative dysfunction was present.

A life table of the outcome of the total population was constructed for 36 patients with a minimum of 5 years' follow-up after initial therapy.[5] Patients lost to follow-up or who died of other causes were included as survivors at the time they were last observed.

RESULTS

Study patients were grouped according to the preoperative status and intraoperative management of the facial nerve (Table 1). The nerve was preserved in almost one third (11 of 35) of the patients with a normally functioning seventh nerve prior to tumor removal. Among these 11 patients (group 1, Table 2), four had total parotidectomies with facial nerve dissection, and in no case was the tumor adherent to the nerve. One had a lateral lobectomy, two had excision of the tumor elsewhere without further therapy, and one patient had multiple local excisions and radiotherapy. Three patients had radical excision of recurrences. Less than 40% of the patients (four) in group 1 received postoperative radiation therapy, and among the seven patients alive without disease, one patient received radiotherapy (Table 2). Mortality varied widely in this group. Three of 11 patients died of disease after follow-up periods ranging from 1 to 29 years, seven were alive without disease 1 to 24 years postoperatively, and one was alive with disease 1 month postoperatively.

TABLE 1. MANAGEMENT OF FACIAL NERVE (N = 43)

	Function of Nerve Preoperatively	*Disposition of Nerve*
Group 1 (n = 11)	Normal	Intact
Group 2 (n = 24)	Normal	Partially or totally removed
Group 3 (n = 8)	Dysfunction	Removed

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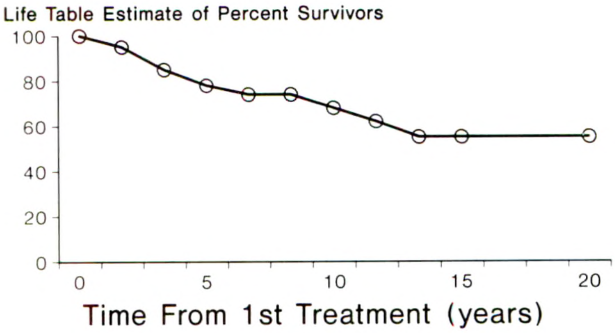
TABLE 2. OUTCOME OF TREATMENT (N = 43)

	Patients With Disease		*Patients Without Disease*	
	Alive	*Dead*	*Alive*	*Dead*
Group 1 (n = 11)	1	3	7	
Group 2 (n = 24)	4	5	14	1
Group 3 (n = 8)	3	4	1	

Group 2 comprised 24 patients who had resection of the nerve without clinical evidence of facial nerve involvement. Intraoperative findings necessitated surgical radicality in this group. Eleven patients had the most radical operation that could reasonably be attempted for cure. This included radical parotidectomy, facial nerve resection, and extensive resection of the surrounding tissue. Five patients had postoperative radiotherapy, two for cancer involving the facial nerve in the temporal bone. Six of these patients had facial nerve rehabilitation at the time of resection. Ten patients in group 2 underwent a lesser procedure that included radical parotidectomy, resection of the facial nerve, and upper neck dissection. Two of these patients received postoperative radiotherapy. The remaining three patients in group 2 had total or lateral lobectomy with sacrifice of the facial nerve. The upper division of the nerve was preserved in one patient; the two others had facial nerve rehabilitation. Five of 24 patients in this group died of their disease from 3 to 13 years, and 13 had no evidence of disease from 1 to 30 years.

In group 3, clinical involvement of the facial nerve by the cancer was evident preoperatively. Four patients had extremely radical excisions, and four had total parotidectomy, facial nerve resection, and upper neck dissection. All of the former and half of the latter had postoperative radiotherapy.

Determinate survival rates from the time of the initial therapy of 36 patients with a minimum of 5 years' follow-up were 83% at 5 years and 53% at 20 years (see Figure).



Life-table for patients with adenoid cystic carcinoma of parotid gland. Numbers of patients in study alive and under observation at entry and at 5, 10, 15, and 20 years were 36, 32, 16, 6, and 5, respectively.

DISCUSSION

Dysfunction of the facial nerve is found commonly among patients with adenoid cystic carcinoma of the parotid gland. In this series, 18% of patients had evidence of facial nerve involvement by cancer prior to definitive therapy; this finding is similar to the experience of others.[1-4] Batsakis[6] stated that tumor growth within the perineurium occurs in all adenoid cystic carcinomas larger than 1 cm. Ballantyne et al[7] have pointed out that in general, malignancies may involve the nerve without dysfunction. Four patients in this series had gross involvement of the seventh nerve without preoperative paresis.

Involvement of the seventh nerve by parotid cancers, in general, has been an indicator of a poor prognosis.[8,9] Spiro et al[4] reported that among 35 patients with adenoid cystic carcinoma of the parotid glands, treatment failed when tumor-related facial nerve dysfunction was evident initially. Among the patients in our series with preoperative facial nerve dysfunction, the 5-year survival of 55% fell to 22% at 10 years, with one patient living 12 years postoperatively without evidence of disease. Surgical radicality followed by postoperative radiotherapy appears to have resulted in improved survival in this group.

Among 47 cases of adenoid cystic carcinoma of the parotid gland analyzed by Seaver and Kuehn,[3] lateral lobectomy was performed, except when obvious cancer invasion necessitated total parotidectomy and sacrifice of the facial nerve. Three patients received radiotherapy alone. The determinate cure rate at 15 years was 21.4%. Spiro et al[4] managed 35 patients with adenoid cystic carcinoma of the parotid gland surgically. Lateral lobectomy with facial nerve dissection was performed when the cancer was localized to the lateral portion of the gland. The seventh nerve was sacrificed in five patients with subtotal and eight patients with total parotidectomy. Among 28 patients eligible for analysis, 29% were considered cured at 10 years. Differences in statistical methods preclude comparison of survival in our series to those cases mentioned above. Our results, however, support the concept of selectively sparing the facial nerve (Table 2).

The principles of management of adenoid cystic carcinoma in this series include the following.

1. When the facial nerve is not clinically involved and is found to be free of tumor intraoperatively, it is considered relatively safe to spare the nerve. (Lateral lobe or total parotidectomy was performed in these cases.)
2. When the facial nerve is not clinically involved, it is sacrificed when en bloc excision including the nerve is necessary to remove the tumor; gross pathologic changes in the nerve, such as thickening or a knobby appearance, are noted intraoperatively; or tumor is adherent to the nerve.

(Three distinct operations were performed on these patients: radical parotidectomy and extensive resection of the surrounding tissue, variously including partial mandibulectomy, infratemporal space resection, mastoidectomy, partial palate resection, temporal bone resection, and, when appropriate, radical neck dissection; radical parotidectomy, facial nerve resection, and upper neck dissection; and superficial or total parotidectomy with sacrifice of the facial nerve.)

3. When the facial nerve is clinically involved with cancer, it is resected.
4. Total parotidectomy with or without facial nerve resection and upper neck dissection is used when the operation is done for cure and there is a reasonable cuff of tissue around the cancer, or if the operation is palliative. In such cases in this series, physiology and aesthetics were considered vis-à-vis local control of the disease. Old and young patients who were better able to deal with a protracted clinical course of local recurrences and metastases were offered this alternative to ablative surgery.
5. Facial nerve rehabilitation by nerve grafting, muscle transfer, nerve crossover, or static systems is done whenever anatomically possible at the time of nerve resection.
6. Established criteria for the use of radiotherapy in cancer of the parotid are followed. Among the indications[10] are high-grade cancers; recurrent cancers; deep lobe cancers; gross or microscopic residual disease; tumor adjacent to the facial nerve; regional neck metastases; invasion of muscle, bone, skin, nerves, or any extraparotid extension; and any T3 parotid cancers.

CONCLUSIONS

This review of 43 cases of adenoid cystic carcinoma of the parotid gland focused on the management of the facial nerve in surgically treated patients. Findings underscore that there is no single management of adenoid cystic carcinoma of the parotid gland. The literature and indeed this study include a variety of plans of treatment for high-risk patients. The philosophy of treatment reflected in this study focuses on an operation with the aim of removing all gross cancer, selective sparing of the facial nerve, the immediate rehabilitation of the facial nerve when this is realistic, and the use of postoperative radiotherapy when indicated. The data derived from this analysis of these cases give strong support to this concept of management, in the incidence of cure and long-term survivability with good quality of life.

ACKNOWLEDGMENTS — We would like to thank Michael Selzer, Department of Biostatistics, The University of Iowa College of Medicine, Iowa City.

REFERENCES

1. Blanck C, Eneroth CM, Jacobsson F, Jakobson PA. Adenoid cystic carcinoma of the parotid gland. Acta Radiol Ther Phys Biol 1967;6:177-96.

2. Cummings CW. Adenoidcystic carcinoma (cylindroma) of the parotid gland. Ann Otol Rhinol Laryngol 1977;86:280-92.

3. Seaver PR Jr, Kuehn PG. Adenoid cystic carcinoma of the salivary glands. A study of ninety-three cases. Am J Surg 1974; 128:512-20.

4. Spiro RH, Huvos AG, Strong EW. Adenoid cystic carcinoma of salivary origin. A clinicopathologic study of 242 cases. Am J Surg 1974;128:512-20.

5. Elisa LT. Statistical methods for survival data analysis. Belmont, Calif: Lifetime Learning Publications, 1980.

6. Batsakis JG. Tumors of the head and neck. Clinical and pathological considerations. Baltimore: Williams and Wilkins, 1979:1-75.

7. Ballantyne AJ, McCarten AB, Ibanez MI. The extension of cancer of the head and neck through peripheral nerves. Am J Surg 1963;106:651-67.

8. Conley J, Hamaker RC. Prognosis of malignant tumors of the parotid gland with facial paralysis. Arch Otolaryngol 1975; 101:39-41.

9. Eneroth CM. Facial nerve paralysis. A criterion of malignancy in parotid tumors. Arch Otolaryngol 1972;95:300-4.

10. Guillamondegui OM, Byers RM, Luna MA, Chiminazzo H, Jesse RH, Fletcher GH. Aggressive surgery in treatment for parotid cancer: the role of adjunctive postoperative radiotherapy. Am J Roentgenol 1975;123:49-54.

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OSTEOMYELITIS OF THE FRONTAL BONE

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Osteomyelitis of the frontal bone and its complications remain a diagnostic and therapeutic challenge to the head and neck surgeon. This paper will deal with the etiology, pathogenesis, diagnosis, and treatment of osteomyelitis of the frontal bone, and its complications and sequelae. Special emphasis is placed on techniques for repair of forehead defects.

KEY WORDS — forehead, frontal bone, osteomyelitis, sinusitis.

ETIOLOGY

Osteomyelitis of the frontal bone may occur with the first episode of frontal sinusitis or during an acute sinus infection superimposed on chronic frontal sinus disease. It has long been recognized that many of these patients suffer from allergic sinusitis. External trauma to the forehead, especially in young patients during sports, at the time of a bacterial sinusitis can precipitate acute osteomyelitis of the frontal bone. Swimming, and especially diving, with an acute bacterial sinusitis can precipitate acute frontal sinusitis that progresses to osteomyelitis.

A variety of bacteria can be found associated with osteomyelitis of the frontal bone. The most common are *Staphylococcus aureus* and *Streptococcus hemolyticus*. In our experience, *Staphylococcus epidermidis (albus)* is often associated with the more chronic, slow, and insidious form of osteomyelitis of the frontal bone.

PATHOGENESIS

The veins of the mucous membrane of the frontal sinus communicate with the diploë of the outer and inner tables of the frontal sinus. It is quite probable that at least a degree of osteitis is associated with most cases of frontal sinusitis.

Inner Table. Osteomyelitis of the inner table of the frontal sinus spreads or extends to cause meningitis or to form an epidural, subdural, or brain ab-

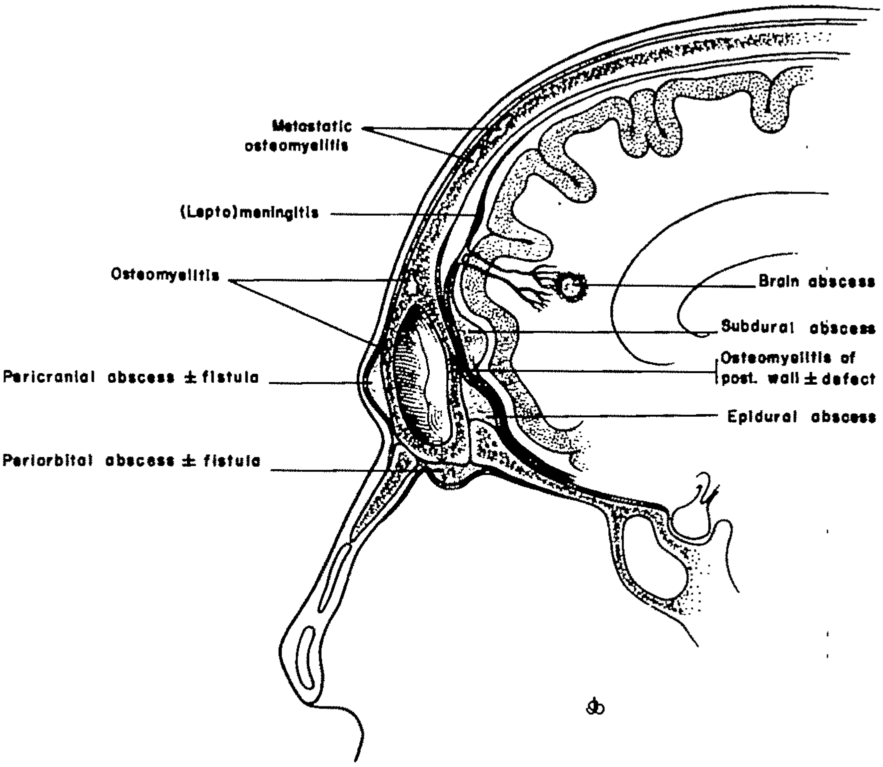

Fig 1. Sketch illustrating pathogenesis of osteomyelitis of frontal bone and extension of disease beyond sinus walls.

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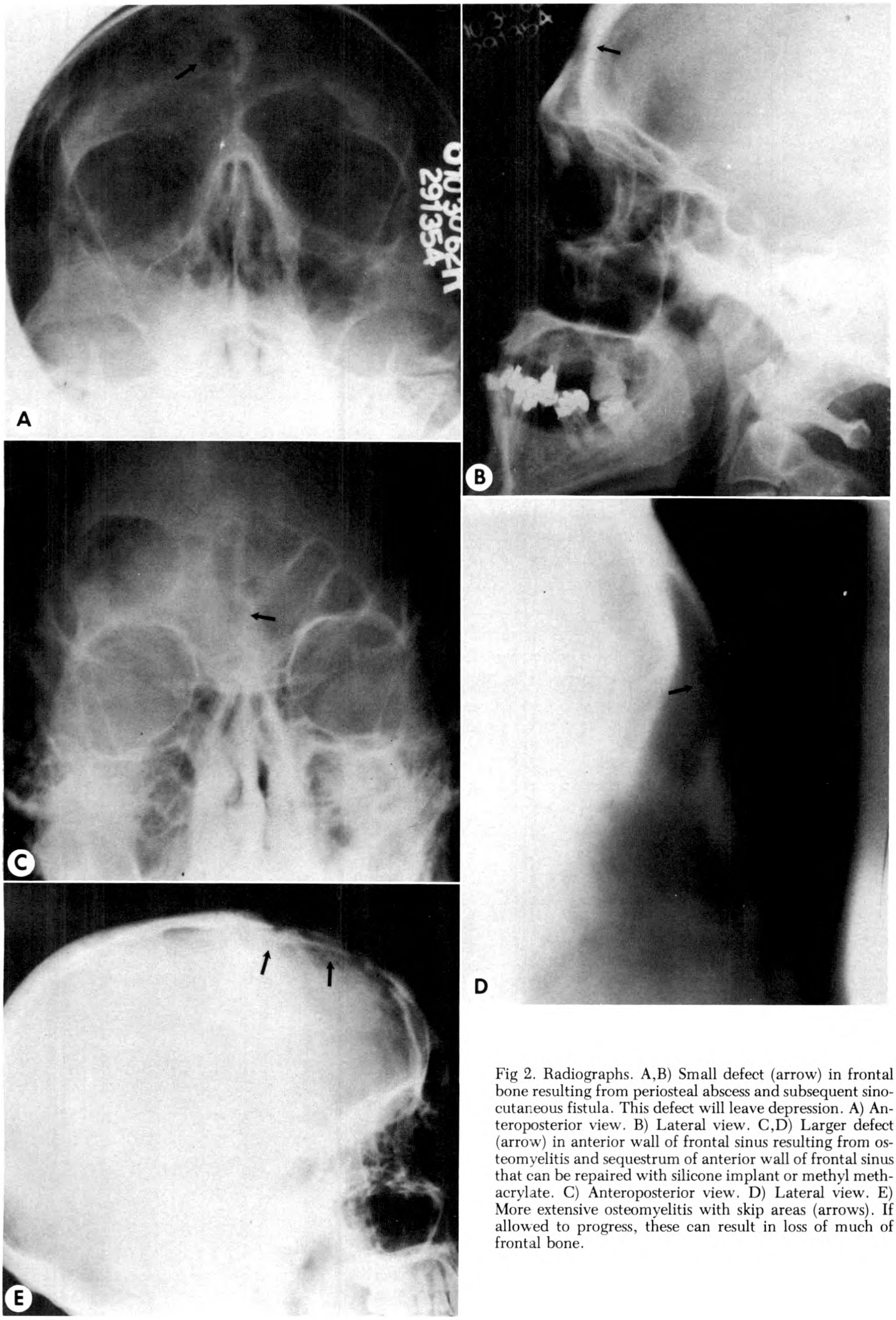

Fig 2. Radiographs. A,B) Small defect (arrow) in frontal bone resulting from periosteal abscess and subsequent sinocutaneous fistula. This defect will leave depression. A) Anteroposterior view. B) Lateral view. C,D) Larger defect (arrow) in anterior wall of frontal sinus resulting from osteomyelitis and sequestrum of anterior wall of frontal sinus that can be repaired with silicone implant or methyl methacrylate. C) Anteroposterior view. D) Lateral view. E) More extensive osteomyelitis with skip areas (arrows). If allowed to progress, these can result in loss of much of frontal bone.

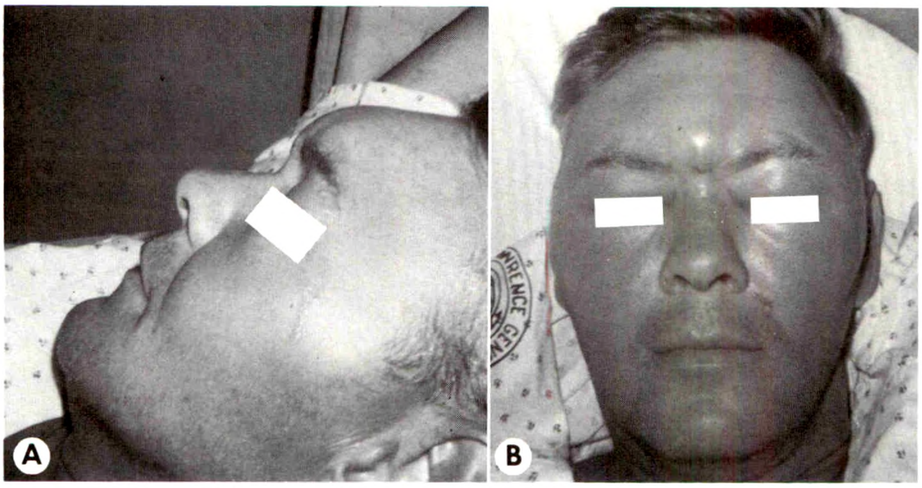

Fig 3. Rather typical picture of patient with Pott's puffy tumor with pitting edema and edema of eyelids. A) Lateral view. B) Frontal view.

scess (Fig 1). In a chronic process there may be no signs or symptoms of meningitis because of arachnoid adhesions.

Outer Table. Basically, there are two types of osteomyelitis of the outer table. The localized type of osteomyelitis (Fig 2A,B) of the anterior wall can progress to periosteal abscess and a sinocutaneous fistula. A sequestrum of the anterior wall may occur that will result in a larger defect (Fig 2C,D).

The spreading type of osteomyelitis of the outer table of the frontal bone results from a thrombophlebitis of the diploic veins. Usually a larger area of the front wall of the frontal sinus is involved. There may be skip areas and multiple sites of osteomyelitis (Fig 2E).

DIAGNOSIS

Outer Table. Acute osteomyelitis of the outer table of the frontal sinus is accompanied by pain and tenderness of the forehead. There is most often swelling of the soft tissues of the forehead. This swelling is pitting edema (Pott's puffy tumor) and is the result of periostitis (Fig 3). Edema of the upper eyelid(s) is most often present.

Chronic osteomyelitis of the outer table of the frontal sinus also can cause pain and tenderness. This tenderness is more likely to be localized. A sinocutaneous fistula of the forehead is not uncommon. A sino-orbital fistula results from extension of disease from the frontal sinus through the roof of the orbit. This may progress to an abscess of the upper lid and a chronic fistula is this area.

Routine radiography, polytomography, and computed tomography are essential for the proper evaluation of osteomyelitis of the frontal bone. In any given active case of osteomyelitis, the extent of

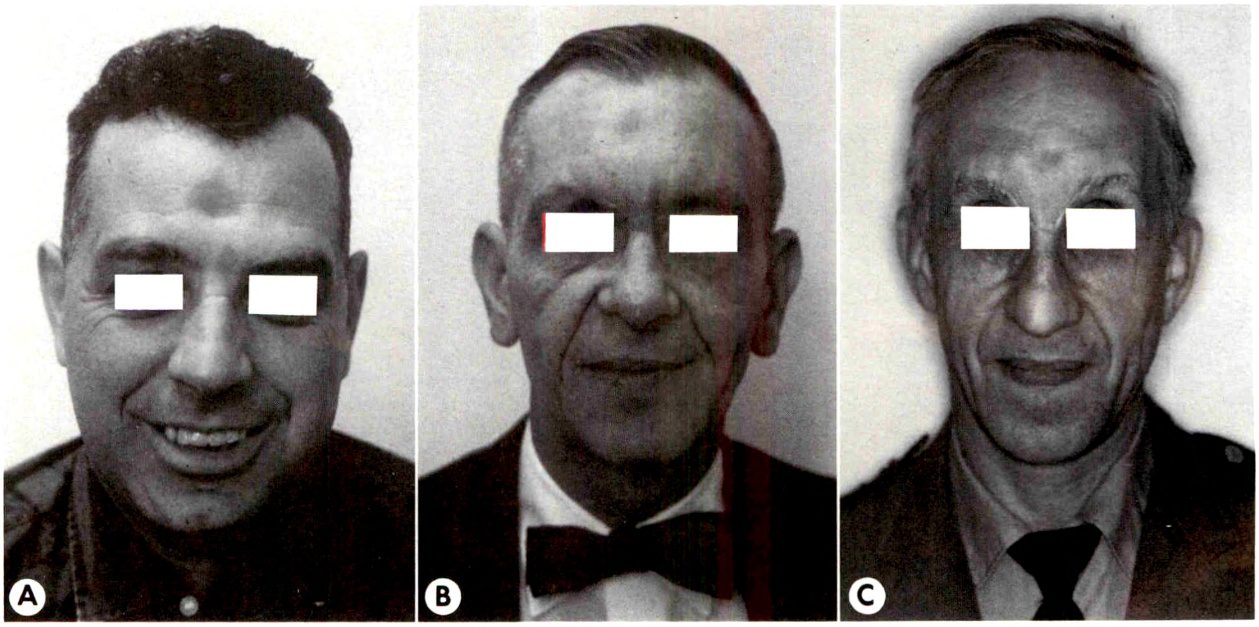

Fig 4. Three patients with almost identical defects resulting from sinocutaneous fistulas. Possibly these defects could have been avoided if, at time of osteoplastic adipose tissue obliteration operation, sinus had been slightly overobliterated with adipose tissue and defect had been covered with periosteal flap. A) Case 1. B) Case 2. C) Case 3.

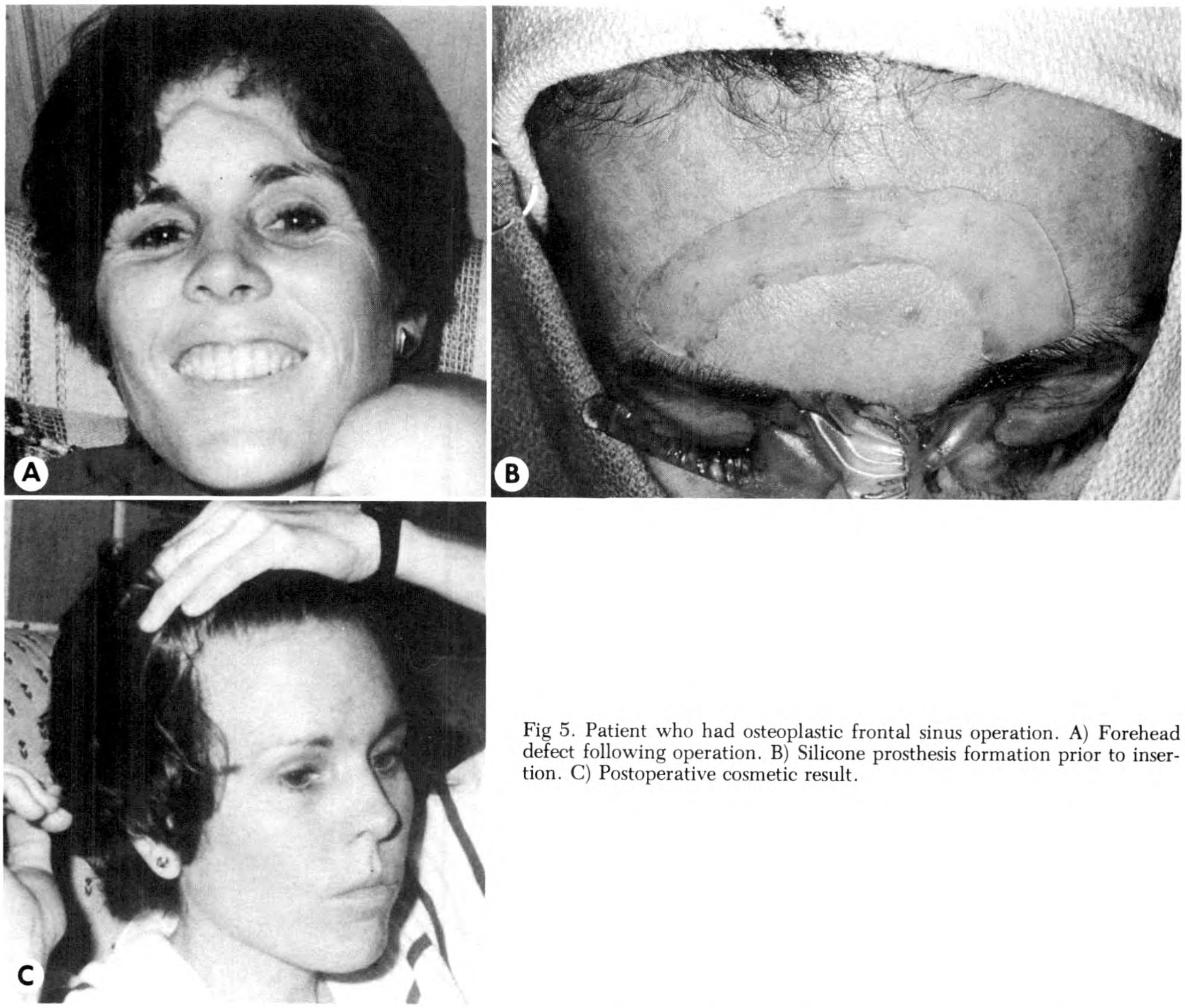

Fig 5. Patient who had osteoplastic frontal sinus operation. A) Forehead defect following operation. B) Silicone prosthesis formation prior to insertion. C) Postoperative cosmetic result.

the abnormal radiographic findings may lag 1 to 2 weeks behind the clinical progress of the disease. Therefore, the estimation of the severity of each case and the required magnitude of appropriate treatment should be based primarily upon clinical judgment.

Technetium and gallium scanning of the head are used to confirm the diagnosis of osteomyelitis of the frontal bone. These tests demonstrate the extent of the disease and the response to antibiotic therapy, and are used as a guide to the needed duration of antibiotic therapy.

Inner Table. Involvement of the inner table can be suspected only when there is a complication such as meningitis or an epidural, subdural, or frontal lobe abscess. A lumbar puncture and study of the spinal fluid can be diagnostic. A CT scan usually is sufficient for proper diagnosis. Magnetic resonance imaging is very useful for the diagnosis of intracranial extension of disease.

TREATMENT

Acute osteomyelitis of the frontal bone is best treated by performing a trephination through the medial aspect of the floor of the frontal sinus. This provides drainage and also allows the surgeon to obtain material for culture and sensitivity tests. Intravenous antibiotics are used as indicated by the report from the bacteriology laboratory. Both CT scanning of the frontal sinus and technetium and gallium scanning of the head are extremely useful as a guide for the duration of antibiotic therapy. The duration of antibiotic therapy is usually about 6 weeks.

Intracranial extensions of the disease are best treated in conjunction with a neurosurgeon using the frontal craniotomy approach. It is our preference to treat the frontal sinus disease several weeks following completion of therapy for the intracranial extension. The frontal sinuses are obliterated with adipose tissue by use of the osteoplastic flap technique.

Subacute and chronic osteomyelitis of the frontal sinus are treated with 2 weeks of intravenous antibiotic therapy prior to an osteoplastic adipose tissue obliteration operation. The intravenous antibiotics

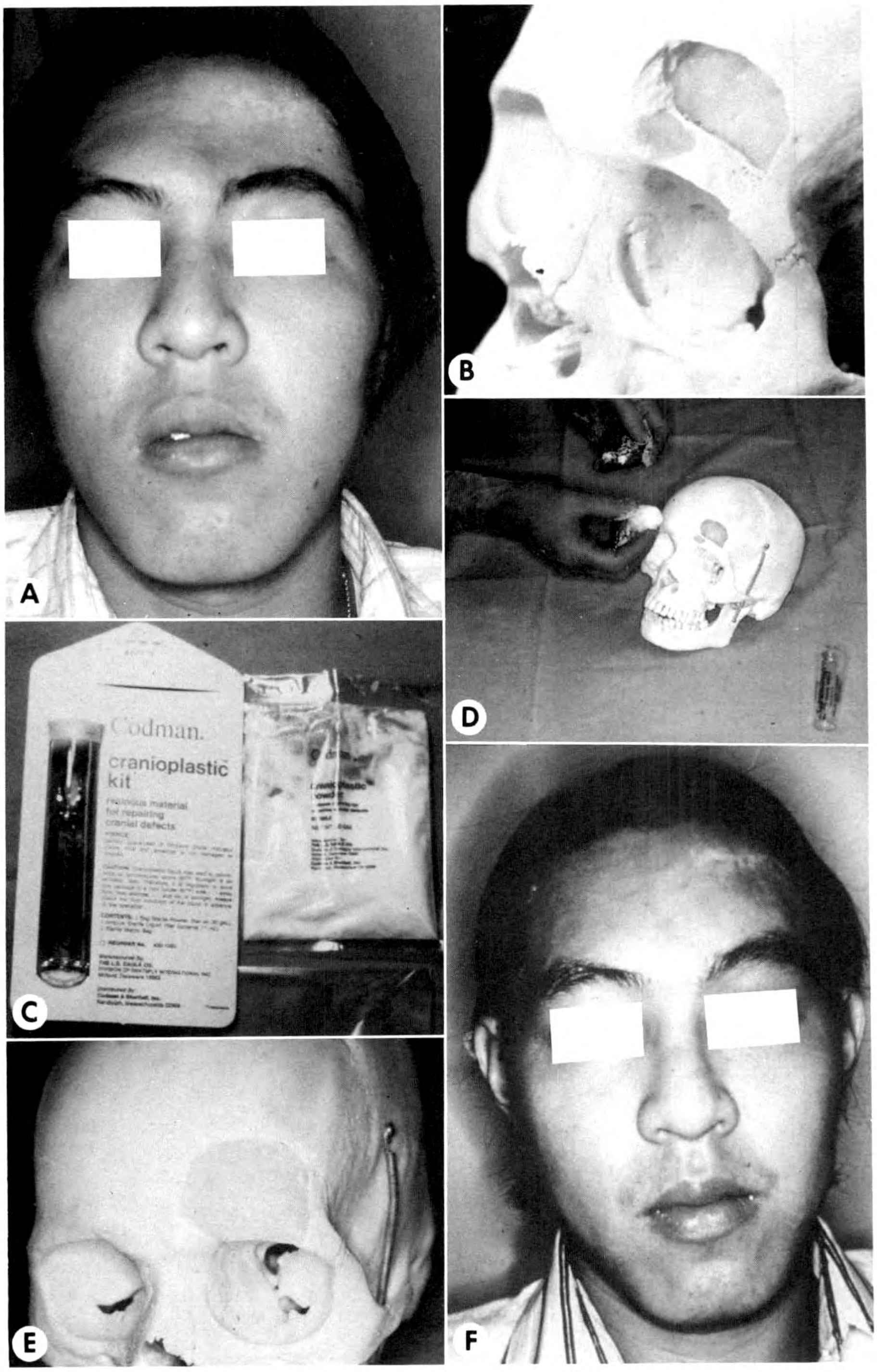

Fig 6. Repair of defect. A) Patient who lost large portion of front face of left frontal sinus and also left supraorbital rim. B) Simulated defect similar to that of patient in A. Osteomyelitic bone has been removed, and communication to nasal cavities has been obliterated with adipose tissue. Orbital rim is for most part absent. Defect on this skull includes anterior wall of frontal sinus and supraorbital rim as shown. Nasofrontal communication has been obliterated. C) Cranioplasty kit (Codman). Components of kit have been mixed in bowl, and methyl methacrylate allowed to become semisolid. At this point it is applied to defect and sculptured so that it slightly overcorrects defect. It then is removed and allowed to cool. D) Once methyl methacrylate has cooled, it is reapplied to defect and contoured with rotating cutting bur. E) Drill holes have been made in both implant and surrounding bone so that implant can be secured in place with stainless steel wires. F) Patient in A following reconstruction of left forehead and supraorbital rim.

are continued 4 to 6 weeks following this operation. Often it is advisable to continue oral antibiotics for an additional 4 weeks after completion of intravenous therapy.

TREATMENT OF DEFECTS OF FRONTAL BONE RESULTING FROM OSTEOMYELITIS

Small defects from localized osteomyelitis of the anterior wall of the frontal sinus can be treated primarily at the time of the osteoplastic adipose tissue obliteration operation. The diseased bone is resected until healthy bone is encountered. The osteoplastic frontal sinus operation is completed with sufficient adipose tissue so that it bulges through the defect in the anterior wall of the frontal sinus. Finally, a periosteal (pericranial) flap is rotated and sutured over the defect and fat.

Small defects that persist after completion of therapy should not be disturbed for a few months (Fig 4A,B). There are many ways to repair these defects. A Teflon injection is effective. A small silicone implant can be fashioned to the size and shape of the defect and inserted through a small tunnel by way of a horizontal forehead skin incision.

To create a silicone implant, an impression is made of the forehead with room temperature vulcanizing silicone or moulage. A positive mold then is made from this impression. Finally, medical grade silicone is used to fashion the implant. The implant and mold then are placed in an oven to be vulcanized at 177°C for half an hour. After the vulcanizing process, the implant is removed from the mold and cured for an additional 2 hours at 177°C. It is sterilized in the autoclave prior to surgery. Figure 5B shows such an implant about to be inserted by way of a small horizontal incision. Figure 5A,C shows the preoperative and postoperative photographs of a patient who was treated with this technique. If one does not have the time or skill to make this implant, a prosthodontist can make it readily.

Major defects of the frontal bone (Fig 6A) with or without involvement of the orbital rim or floor of the frontal sinus are best treated in two stages. The osteomyelitic bone is debrided, and the remainder of the frontal sinus complex is obliterated with adipose tissue so that there is no communication with the nasal cavity (Fig 6B). Then, in 2 to 3 months, the defect is repaired.

A defect in the frontal bone that included the supraorbital rim and frontal sinus, similar to that in the patient in Fig 6A, is shown in the skull specimen in Fig 6B. The frontal sinus first is prepared and obliterated with adipose tissue. The cranioplasty kit (Codman) is shown in Fig 6C. The liquid is added to the powder, which has been placed in a stainless steel bowl. This is agitated with a tongue blade until it becomes a semisolid. The instructions advise that the soft methyl methacrylate be placed between two sheets of plastic, rolled out with a glass ampoule, and placed over the frontal defect. The methyl methacrylate can be contoured when in place or after it has been removed (Fig 6D). Drill holes are made in both the skull and the methyl methacrylate so that the implant can be wired in place. It is best to tuck the ends of the wire in the drill holes (Fig 6E). A patient is shown who underwent the above repair (Fig 6F).

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AGE-RELATED MORPHOLOGIC DIFFERENCES IN THE COMPONENTS OF THE EUSTACHIAN TUBE/MIDDLE EAR SYSTEM

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The current study utilized a three-dimensional computer graphics technique to analyze the size, shape, and positional associations of the eustachian tube (ET) cartilage and lumen, the levator veli palatini (LVP) muscle, and the tensor veli palatini (TVP) muscle. Older specimens 7 years and above (n = 13) were compared to young specimens less than 7 years (n = 4). Our results suggest that changes in ET function associated with age could result from size and shape differences in the ET cartilage and changes in the position of the LVP and TVP muscles.

KEY WORDS — eustachian tube cartilage, eustachian tube lumen, levator veli palatini muscle, ontogenesis, tensor veli palatini muscle.

INTRODUCTION

Since the early 1970s, researchers have suspected that otitis media with effusion (OME) was the result of functional eustachian tube (ET) obstruction.[1,2] Recently, several experimental studies have demonstrated that functional ET obstruction and OME were associated with compromised efficiency in one of the ET system structures (ie, tensor veli palatini [TVP] muscle).[3-5] The conclusions of these experimental investigations have posited a primary role of underlying morphologic deficiencies in OME causation. Several clinical investigations, moreover, have revealed that both the incidence of OME and tubal functioning efficiency undergo ontogenetic changes, and morphologic variations in the ET system's components may be implicated.[1,2,6] It has not been the purpose of these studies, however, to analyze the ontogenetic morphologic changes that exist in the ET system structures as a means of modeling and investigating the functional ET obstruction/disease pathway.

Several studies have utilized an animal model to produce functional impairment of the ET system's TVP muscle and have supported the "functional eustachian tube obstruction" hypothesis.[3,5] The resultant deficiencies in ET function included an inability to equilibrate applied positive and negative pressures and tubal lumen constriction during swallowing leading to or during bouts of OME.[3,4] Casselbrant et al[4] observed that following temporary paralysis of the TVP muscle, rhesus monkeys developed the symptoms of OME within 8 to 30 days. Normal middle ear ventilatory function returned after the return of TVP muscle function. Similarly, Doyle et al[3] demonstrated that rhesus monkeys exhibited these symptoms after operatively induced clefting of the palate produced a permanently dysfunctional TVP muscle. Clinical investigations of cleft palate and Down syndrome children, two groups exhibiting high incidences of OME, revealed that several of these same functional obstruction symptoms were present.[7,8] Concomitantly, these groups exhibited morphologically deformed craniobasal regions and, by inference, a dysmorphic relationship among the ET system components. Such studies provided supporting evidence that the morphology of the ET system was significantly associated with the occurrence of OME.[2,9,10]

The pathologic consequences of functional ET system obstruction decrease with age — a fact that is indicative of functional changes resulting from ontogenetic morphologic variations. Bluestone,[1] Casselbrant et al,[6] and Holborow[2] noted that a reduction in the prevalence of childhood OME occurred after 7 years of age. This finding was so apparent that otitis media has been termed a disease of infants and young children.[11] Further, Bluestone and Klein[12] noted that healthy children had a higher frequency of poor muscular opening function of the ET than healthy adults, and Bylander et al[13] observed that muscular opening function improved with aging in a sample of healthy children. In spite of the observations from these functional studies, age-related morphologic changes in the size, shape, and spatial relations of the ET system structures have remained beyond the investigative protocols of many middle ear studies. Given the correlation of OME and tubal functioning differences with age, however, any ontogenetic morphologic changes potentially are of primary importance in understanding the structural foundations of OME.

The purpose of this study was to quantify normal age-related changes in the size, shape, and spatial

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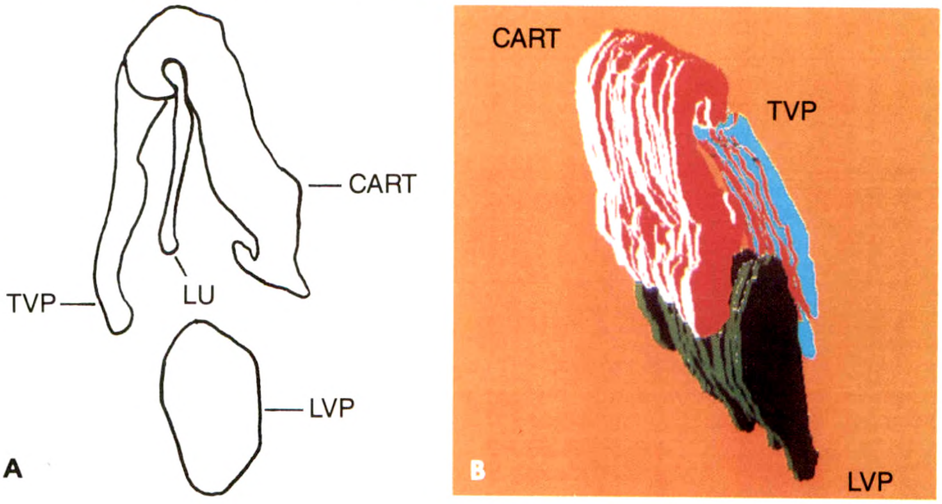

Fig 1. Eustachian tube cartilage (CART), lumen (LU), tensor veli palatini (TVP) muscle, and levator veli palatini (LVP) muscle. A) Boundary tracing of structures in their original spatial relationships. B) Three-dimensional computer representation of sections of structures.

relations of the ET system structures by use of a computer graphics reconstructive technique. This study established the normal morphology and positional associations of the ET system structures and statistically compared young and older human groups.

MATERIALS AND METHODS

This study, focusing on the ET cartilage and lumen and the associated musculature, obtained extended temporal bone specimens and separated them into two groups: older specimens from subjects 7 years of age and above ($n = 13$) and young specimens from subjects less than 7 years of age ($n = 4$). The criterion for inclusion in the adult group was maturation (ie, decreased growth rate) of the anteroposterior length of the ET cartilage. The ET cartilage length exhibited a rapid growth rate prior to age 7, while this rate drastically decreased after age 7.[14,15] By age 7, then, the ET cartilage attained adult length. It was interesting to note that this age division corresponded to the age at which there was a significant reduction in the occurrence of otitis media.[1,2,6]

Histologic and photographic processing and graphic conversion of the specimens was necessary before computer-generated structures could be extracted and analyzed.[14,16] Histologic preparation of the extended temporal bone specimens began with decalcification and embedding in percentage celloidin solutions. Following sagittal microtome sectioning at 20 to 30 μm, serial tenth sections were hematoxylin and eosin–stained and mounted on glass slides. Each slide was photographed with Kodak Pan X film and a light microscope with a camera attachment, beginning with the first appearance of the tubal cartilage and ending with the last slide in which it was present. The negatives were transformed into digitized images by use of an Optronics 6300 rotating drum scanner that converted transmitted gray-level light intensity to an integer producing a digitized image of approximately a quarter of a million data points. Images were projected on a Ramtec display screen, aligned to correct for displacement errors, and stored on the disk of a PDP 11/55 computer.

Structural extraction and reconstruction included the ET cartilage and lumen and portions of the levator veli palatini (LVP) and TVP muscles that occur along the course of the ET cartilage. The extractions were obtained by tracing the boundaries of the structure and maintaining them in their original spatial relationships (Fig 1A). Boundary files subsequently were combined, and intermediate sectional boundaries automatically were interpolated to produce a three-dimensional reconstructed representation of the structures (Fig 1B).

Several quantified measures from the computer-generated structures were obtained for each structure: total volume, cross-sectional area, and x and y coordinates of the center of gravity (centroid) and of the second-level moment. The sum of the areas within the boundary tracings, in addition to the interpolations of the areas of the intervening sections that were not digitized or prepared histologically, was used to calculate the total volume of each structure. The center of gravity, rather than the edge of the structure, was used to calculate distances, because it was a clearly defined point that satisfied the requirements of repeatability and comparability within and between specimens. The x and y coordinates of the second-level moment were used to analyze the shape of the structures in the system. Second-level moment coordinates represented the energy required to produce rotation around the center of gravity and were physically related to the maximum and minimum axes through the center of gravity, thereby representing an object's length and width. The ratio of these coordinates (length/width) has been called the aspect ratio.[14,15] The aspect ratio, structural volume, cross-sectional area, and distances between centers of gravity were utilized to compare the four structures statistically in the adult versus the immature

TABLE 1. ASPECT RATIO, AREA, AND VOLUME (MEAN ± SD)

	Older	*Young*	t	*p*
Cartilage				
Aspect ratio	3.77 ± 1.13	2.81 ± 0.47	2.81	< .05
Area (cm^2)	0.15 ± 0.07	0.05 ± 0.03	3.83	< .05
Volume (cm^3)	0.27 ± 0.14	0.10 ± 0.08	3.17	< .05
Lumen				
Aspect ratio	20.90 ± 13.90	9.30 ± 5.80	2.40	< .05
Area (cm^2)	0.03 ± 0.15	0.01 ± 0.01	3.83	< .05
Volume (cm^3)	0.04 ± 0.03	0.03 ± 0.01	3.22	< .05
Levator veli palatini muscle				
Aspect ratio	3.13 ± 1.39	7.17 ± 8.69	0.69	NS
Area (cm^2)	0.11 ± 0.06	0.04 ± 0.15	4.24	< .05
Volume (cm^3)	0.16 ± 0.13	0.05 ± 0.03	3.22	< .05
Tensor veli palatini muscle				
Aspect ratio	15.40 ± 14.50	8.10 ± 6.50	1.41	NS
Area (cm^2)	0.07 ± 0.05	0.05 ± 0.03	1.22	NS
Volume (cm^3)	0.08 ± 0.07	0.06 ± 0.04	0.67	NS

NS — not significant.

TABLE 2. DISTANCE BETWEEN STRUCTURAL CENTERS OF GRAVITY (MEAN ± SD)

	Distance (μm)			
	Older	*Young*	t	*p*
ET cartilage to LVP muscle	6,335 ± 1,135	4,285 ± 1,249	3.09	< .01
ET cartilage to TVP muscle	4,155 ± 1,044	3,215 ± 797	1.64	NS
ET cartilage to ET lumen	1,875 ± 992	1,365 ± 375	0.98	NS
LVP muscle to TVP muscle	5,750 ± 1,384	2,584 ± 1,284	4.06	< .01
LVP muscle to ET lumen	6,015 ± 925	2,891 ± 1,835	4.69	< .01
TVP muscle to ET lumen	3,030 ± 1,040	1,603 ± 747	2.53	< .05

ET — eustachian tube, LVP — levator veli palatini, TVP — tensor veli palatini, NS — not significant.

groups. Mean values for the aspect ratio, cross-sectional area, and distance measures were calculated by first finding the average value throughout the course of the specimen, and then using these values to obtain and report a group mean. Group standard deviations, Student's *t* values, and probability levels resulting from the statistical comparisons are reported in Tables 1 and 2.

RESULTS

Nondistance Structural Comparisons. The ET cartilage showed significant age-related variation in both size and shape. Mean total volume and mean cross-sectional area were significantly larger in the older group, indicating grossly larger ET cartilages in these specimens (Table 1). The shape of the cartilage also differed between groups. The older group exhibited a significantly larger aspect ratio, suggesting a more elongate, relatively thinner structure than that of the young group. Figure 2A indicates that this shape was maintained throughout the specimens with little variation. The average aspect ratio in the young group was smaller in value, reflecting a shorter and broader ET cartilage. In Fig 2B it can be seen that the shape of the immature cartilage changed throughout its length. In the 40% to 80% region of the cartilage, the aspect ratio approached 1, indicating a circular shape, while in the 0% to 40% and 80% to 100% areas, it more closely approached the older value, reflecting an elongate shape.

The lumen was similarly larger in the older specimens, as evidenced by the significantly larger volume and cross-sectional area (Table 1). The difference in lumen shape between the older and young groups reflected the results obtained for the ET cartilage, in that the aspect ratio of the older lumen was significantly larger than that of the young lumen, indicating a longer and thinner structure in the older group. In both the older and the young groups, conversely, the shape of the lumen remained constant throughout the specimen.

Ontogenetic size differences in the LVP existed between the two groups. As seen in Table 1, mean total volume and mean cross-sectional area of the LVP muscle was significantly larger in the older group than in the young group. Both the older and young groups had low aspect ratio values, indicative of an oval LVP muscle. The shape of the LVP muscle did not differ between groups, nor did it change through the course of the specimen.

The TVP muscle did not differ significantly between groups in volume, cross-sectional area, or shape (Table 1). In both groups the aspect ratio was high, indicating a TVP muscle that was long and narrow throughout the specimen.

Structural Distance Comparisons. There were no significant differences between groups in the distance between the ET cartilage and TVP muscle or the ET cartilage and lumen (Table 2).

All three measures of LVP muscle distance (LVP muscle to cartilage, LVP muscle to TVP muscle, and LVP muscle to lumen) were significantly greater in the older group than in the young group, indicating that in the older group the LVP muscle was more separated from the ET system than in the young group.

The TVP muscle to lumen and, as noted, the TVP muscle to LVP muscle distance was significantly greater in the older group than in the young group, although the distance between the TVP muscle and the ET cartilage did not differ between groups.

DISCUSSION

Clinical observations of the decline in the occurrence of OME at 6 to 7 years of age and results from previous studies demonstrating a morphologic growth change that occurs in the ET system at 7 years of age were used to justify the age-group cate-

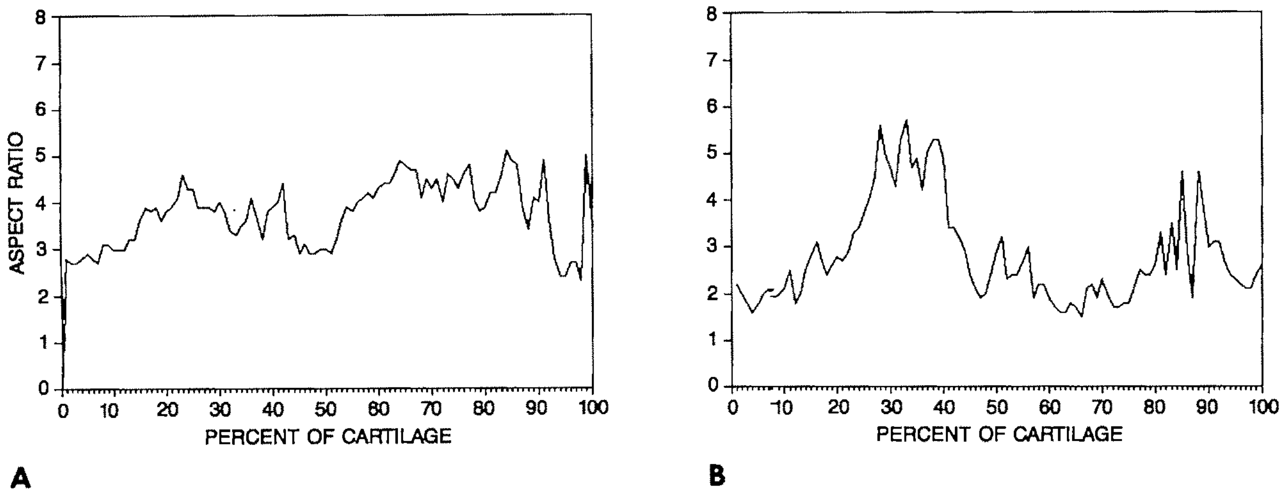

Fig 2. Cartilage aspect ratio plotted against percent of cartilage length. A) Older group. B) Young group.

gories selected for this study. The decision to divide the sample into two groups was based primarily on an observed age-related change in the occurrence of OME. Bluestone,[1] Holborow,[2] and Casselbrant et al[6] have noted a decrease in the susceptibility of OME after age 7. Bylander et al[13,17] demonstrated ontogenetic functional efficiency differences in healthy children by reporting that the muscular opening function of the ET was not only poorer in children than in adults, but also poorer in younger children (3 to 5 years) than in older children (6 to 12 years). It follows that changes in ET function and the presence of OME may be due, at least in part, to age-related morphologic changes that occur between the <7 and ≥7 age groups. The separation of age groups was based secondarily on the growth of the ET cartilage.[14,15] The rate of change of cartilage length (slope of regression line) approached zero at age 7, and subsequently, the young group included specimens 0 to 6 years of age, and the older group, specimens 7 years and above.

The ET cartilage changed significantly in both size and shape from the young group to the older group, and this ontogenetic variation, in conjunction with a shift in the relative position of the TVP muscle, is posited as a mechanism producing tubal function differences between groups. In the older group, the ET cartilage exhibited both a larger volume and a larger cross-sectional area and was a structure whose aspect ratio indicated relatively long and thin as opposed to short and wide dimensions. The lumen, not unexpectedly, paralleled this pattern, in that both lumen volume and cross-sectional area were significantly larger in the adult group, and the shape of the adult lumen was longer and thinner than that of the immature group.

There is considerable evidence that the TVP muscle is the primary active opener in ET function.[1,4,5,18] While this study found no significant differences in the volume, cross-sectional area, or shape of the TVP muscle, three important distance measures suggested that an age-related superiorly oriented rotation of the TVP muscle relative to the other components of the ET system may occur in the older group. The measurement from the TVP muscle to the lumen, as well as from the TVP muscle to the LVP muscle, revealed an increased distance from the young group to the older group, while the TVP muscle to ET cartilage distance was not significantly different. This angulation of the TVP muscle relative to the ET cartilage, in conjunction with a thinner, more elongate ET cartilage shape, may establish a mechanical efficiency for opening the tube and partially account for ontogenetic changes in tubal function. Empiric observation from the reconstructions supported this idea, suggesting that the ET cartilage centroid was located superiorly toward the head of the structure, that the lumen centroid was more inferiorly located, and that the TVP muscle centroid was centered midway along the structure. Any rotation of the TVP muscle away from the remainder of the ET system initially would affect distance measures from the inferior portion of the TVP muscle and be reflected in distance from the TVP muscle to the LVP muscle and from the TVP muscle to the lumen. The distance from the TVP muscle to the ET cartilage remained unchanged because it involved the superior portion of these two structures — an area of fulcrum activity, not lateral displacement. It has been demonstrated that TVP muscle function has an effect on ET function and subsequently on the occurrence of OME.[4,5] The present study suggested that the difference in ET function in young and older groups is the result of differences in the size and shape of the ET cartilage and in the position of the TVP muscle. If, as appears likely, the TVP muscle is the primary dilator of the ET, the apparent differences in function may result not from changes in the TVP muscle itself, but from a change in the mechanicofunctional relationship between the TVP muscle and a larger, more elongate ET cartilage in the older group, compared to the smaller, more oval cartilage in the young group.

The LVP muscle showed no change in shape between groups, but both volume and cross-sectional area were significantly larger in the older group. In addition, all measures of distance involving the LVP muscle (LVP muscle to cartilage, LVP muscle to TVP muscle, and LVP muscle to lumen) were significantly larger in the older group. This is consistent with Holborow's[2] finding that with increasing age the LVP muscle moves further away from the medial lamina of the ET cartilage. While some have argued against any involvement of the LVP muscle in ET function,[5,18] others have suggested that it has a possible auxiliary role.[2,10,19] Given that the described change in size and position of the LVP muscle with age correlated with a change in ET function, it is possible that the LVP muscle plays some role in ET functioning, if not directly through muscle contraction, then passively through constriction of the system in the young group. This role could not be determined in the present investigation.

In summary, the current study showed significant ontogenetic changes in the following areas.

1. The ET cartilage, lumen, and LVP muscle all evidenced a significantly larger cross-sectional area and volume in the older group.

2. The ET cartilage and lumen showed significant shape changes, with the older specimens having more elongate structures.

3. The distance from the LVP muscle to the other structures in the ET system (TVP muscle, ET cartilage, lumen) was significantly larger in the older group.

4. The TVP muscle showed no significant differences between the young and older groups in size or shape, but the distance from the TVP muscle to the lumen and from the TVP muscle to the LVP muscle was significantly larger in the older group. The evidence indicated an age-related rotated positioning of the TVP muscle relative to the remaining ET system structures, especially the ET cartilage. This, in association with the more elongate shape of the mature ET cartilage, may be ultimately responsible for an adult TVP muscle with a mechanical advantage, an adult ET system with a more efficient tubal opening mechanism, and an adult middle ear with a relatively low incidence of OME.

REFERENCES

1. Bluestone CD. Eustachian tube obstruction in the infant with cleft palate. Ann Otol Rhinol Laryngol 1971;80(suppl 2).

2. Holborow C. Eustachian tubal function: changes throughout childhood and neuro-muscular control. J Laryngol Otol 1975; 89:47-55.

3. Doyle WJ, Ingraham BA, Saad MM, Cantekin EI. A primate model of cleft palate and middle ear disease: results of a one-year post cleft follow-up. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Proceedings of the third international symposium. Philadelphia: BC Decker, 1984:215-8.

4. Casselbrant ML, Cantekin EI, Dirkmaat DC, Doyle WJ, Bluestone CD. Experimental paralysis of tensor veli palatini muscle. Acta Otolaryngol (Stockh) 1988;106:178-85.

5. Cantekin EI, Phillips DC, Doyle WJ, Bluestone CD, Kimes KR. Effect of surgical alterations of the tensor veli palatini muscle on eustachian tube function. Ann Otol Rhinol Laryngol 1980;89(suppl 68):47-53.

6. Casselbrant ML, Brostoff LB, Cantekin EI, Ashoff VM, Bluestone CD. Otitis media in children in the United States. Proceedings of the International Conference on Acute and Secretory Otitis Media. Amsterdam: Kugler Publications, 1986:161-4.

7. Doyle WJ, Reilly JS, Stool SE, Cantekin EI. Eustachian tube function in children with unrepaired cleft palates. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Proceedings of the third international symposium. Philadelphia: BC Decker, 1984:59-62.

8. White BL, Doyle WJ, Bluestone CD. Eustachian tube function in infants and children with Down's syndrome. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Proceedings of the third international symposium. Philadelphia: BC Decker, 1984:62-6.

9. Bluestone CD, Beery QC, Andrus WS. Mechanics of the eustachian tube as it influences susceptibility to and persistence of middle ear effusions in children. Ann Otol Rhinol Laryngol 1974; 83(suppl 11):27-34.

10. Seif S, Dellon AL. Anatomic relationship between the human levator and tensor veli palatini and the eustachian tube. Cleft Palate J 1978;15:329-36.

11. Giebink GS. Epidemiology and natural history of otitis media. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Proceedings of the third international symposium. Philadelphia: BC Decker, 1984: 5-9.

12. Bluestone CD, Klein JO. Otitis media with effusion, atelectasis, and eustachian tube dysfunction. In: Bluestone CD, Stool SE, eds. Pediatric otolaryngology. Philadelphia: WB Saunders, 1983:356-512.

13. Bylander A, Tjernström O, Ivarsson A. Pressure opening and closing functions of the eustachian tube in children and adults with normal ears. Acta Otolaryngol (Stockh) 1983;95:55-62.

14. Siegel MI, Cantekin EI, Todhunter JS, Sadler-Kimes D. Aspect ratio as a descriptor of eustachian tube cartilage shape. Ann Otol Rhinol Laryngol 1988;97(suppl 133):16-7.

15. Siegel MI, Sadler-Kimes D, Todhunter JS. ET cartilage shape as a factor in the epidemiology of otitis media. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Proceedings of the fourth international symposium. Burlington, Canada: BC Decker, 1988:114-7.

16. Kimes KR, Siegel MI, Mooney MP, Todhunter JS. Relative contributions of the nasal septum and airways to total nasal capsule volume in normal and cleft lip and palate fetal specimens. Cleft Palate J 1988;25:282-7.

17. Bylander A, Tjernström O, Ivarsson A, Ingvarsson L. Eustachian tube function in children with and without otologic history. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Proceedings of the third international symposium. Philadelphia: BC Decker, 1984: 56-8.

18. Honjo I, Okazaki N, Kumazawa T. Experimental study of the eustachian tube function with regard to its related muscles. Acta Otolaryngol (Stockh) 1979;87:84-9.

19. Proctor B. Anatomy of the eustachian tube. Arch Otolaryngol 1973;97:2-8.

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SPEECH PATHOLOGY IN GIANT CELL ARTERITIS

REVIEW AND CASE REPORT

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This paper contains a review of the signs and symptoms of giant cell arteritis, especially speech and respiratory manifestations of the disease, which are demonstrated by a new case history. An elderly woman presented with speech that was falsetto, breathy, and marked by downward pitch breaks and phonation breaks. In addition, she had visual loss, headache, edema along the scalp and pharyngeal arteries, polymyalgia rheumatica, elevation of Westergren erythrocyte sedimentation rates, and positive arterial biopsy results. Her speech disorder recurred during an exacerbation. A vascular mechanism is proposed to explain her unusual speech, acute recurrence, and rapid recovery. This explanation (reversible ischemia of the laryngeal musculature) has been proposed by other authors in previous studies.

KEY WORDS — giant cell arteritis, laryngeal ischemia, pharyngeal and tongue claudication, pharyngeal ischemia, speech pathology.

Some of the most fascinating and little-known signs and symptoms of giant cell arteritis are those that involve respiration and speech: manifestations that can affect 9% of such patients as described in only five prior reports. Involvement of the respiratory tree by the above disease was first described in 1969 by Dresser,[1] almost 80 years after the original report of "cranial arteritis" by Hutchinson[2] in 1890. He erroneously ascribed the causation of the newly described disease to a tight hatband. For 42 years there were no further reports, but in 1932 there began an outpouring of descriptions starting with that of Horton et al,[3] who for the first time used the present appellation "temporal arteritis." They first described the disorder and labeled it "granulomatous arteritis." The above authors recognized most of the signs and symptoms of the disease, which are listed in the Table,[1,4-7] but further contributions were made by Gilmour,[8] who proved the generalized arterial nature of the disease and suggested the present-day term "giant cell arteritis." Further significant additions to the syndrome came from Paulley and Hughes[9] and Fauchald et al,[10] who proved the close relationship between polymyalgia rheumatica and giant cell arteritis. Finally, Hamilton et al[4] in 1971 and Huston et al[11] in 1978 published two well-known scholarly epidemiologic, clinical, and pathologic series that spanned 18 and 25 years, respectively. These often-quoted studies summarized past knowledge and added more clinical facts to this protean syndrome. Interestingly, speech and respiratory disorders were not mentioned in either of these exhaustive reviews.

In 1969, about 80 years after Hutchinson's[2] first report, Dresser[1] first described miosis, trismus, painful deglutition, and hoarseness as the presenting symptoms of temporal arteritis in a 79-year-old man; therefore, Dresser was the first to describe speech disorders in arteritis. Between 1969 and 1985, five different works were published concerning respiratory and speech pathology (see Table[1,4-7]). In the past, symptoms and patient complaints have included the following: pharyngeal and laryngeal claudication, described by Hamilton et al,[4] and also by Kelly et al[5]; cough and sore throat, reported by Dresser[1] as well as by Larson et al[6]; and pleuritic pain, also reported by Larson et al. At physical examination, signs that have been reported are hoarseness, described by Dresser[1] and Larson et al[6]; stridor, listed by Larson et al; and edema of the larynx, found by Jennings.[7] Larson et al also made the important observation that a persistent cough in an elderly woman should suggest the diagnosis of giant cell arteritis.

As far as speech pathology is concerned, there have been only two reports that described hoarseness, which involved four patients[1,6]; no other characteristics concerning the quality of speech have been described until now. The 71-year-old woman who is the subject of this present work is therefore the fifth patient with changes in speech that were the presenting signs of giant cell arteritis; she is also the first to be reported with a vocal disorder other than hoarseness.

Physicians who often treat patients with this disease (especially neurologists and rheumatologists) are familiar with the difficulties of diagnosis and the emergency nature of the illness. This is because a large number of patients are threatened with blindness, as well as thromboses of vessels of the brain and other organs that demand immediate steroid therapy. Unfortunately, the clinician must sometimes rely upon his or her clinical suspicion alone because of the following problems: 1) 40 patients with biopsy-proven disease have been re-

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GIANT CELL ARTERITIS AND POLYMYALGIA RHEUMATICA (SIGNS AND SYMPTOMS WITH LABORATORY FINDINGS)

SYMPTOMS

- Headache
- Scalp dysesthesia
- Jaw claudication
- Anorexia
- Tongue claudication
- Myalgia
- Asthenia
- Mood and psychic changes
- Nausea and vomiting
- Angina
- Painful deglutition
- Arthralgia
- Diplopia
- Amaurosis
- Limb claudication
- Neck pain
- Aching joints
- Morning stiffness
- Shoulder girdle pain
- Hip girdle pain

RESPIRATORY SYMPTOMS

- Pharyngeal claudication (Hamilton et al[4])
- Laryngeal claudication (Kelly et al[5])
- Cough (Dresser[1])
- Sore throat (Dresser[1] and Larson et al[6])
- Pleuritic pain (Larson et al[6])
- Voice changes (This report)

SIGNS

- Edema of scalp arteries
- Nodules of temporal vessels
- Cerebrovascular accident
- Amaurosis and retinal ischemia
- Optic neuritis
- Retinal venous occlusion
- Fever
- Edema and pain of jaw muscles
- Ischemia and gangrene of tongue
- Cardiac ischemia and angina
- Cardiac failure
- Trismus
- Miosis
- Synovitis and arthritis
- Weight loss
- Anemia
- Aortic arch syndrome
- Femoral artery occlusion
- Bruits over large arteries
- Cranial nerve palsies
- Raynaud's phenomenon
- Depression and anxiety
- Organic mental syndrome
- Personality changes

RESPIRATORY SIGNS

- Hoarseness (Dresser[1] and Larson et al[6])
- Stridor (Larson et al[6])
- Edema of larynx (Jennings[7])
- Voice changes (This report)

LABORATORY FINDINGS

- Erythrocyte sedimentation rate >55 mm/h
- Normochromatic, normocytic anemia
- Leukocytosis
- Elevated serum alpha globulin
- Elevated enzymes
  - Alkaline phosphatase
  - SGOT
  - SGPT
- Positive arterial biopsy results
- Positive laryngeal biopsy results (Jennings[7])

ported with low erythrocyte sedimentation rates (ESRs), proving that it is not always a reliable test,[5,12-15] and 2) disease proven by positive arterial biopsies varies from 24% to 60%, and at most hospitals is below 50%.[4,10,16-18] This failure to have one consistent reliable test makes giant cell arteritis difficult to diagnose and manage. Clinicians therefore are forced on occasion to begin steroids as a trial of therapy, on the basis of the clinical history and the results of a physical examination, because it is dangerous to delay. Therefore, the conundrum exists that combines the dangers of ill-advised steroid therapy, compared with the dangers of a missed diagnosis. Any physician who treats patients with arteritis will be aided not only by laboratory results, but by signs and symptoms, such as those reported in this summary. At the present time, some clinicians may not be familiar with voice and respiratory disorders in arteritis, because reports are rare. As an example, diseases of respiration and speech have been found to be the presenting symptoms in only 4% of patients with giant cell arteritis, but will appear sometime during the course of the disease in 9%.[6]

The purpose of this work is twofold: to review signs and symptoms of arteritis that affect the respiratory tree, and also to encourage researchers to advance the understanding of giant cell arteritis by exhaustive studies of speech and respiration. Future studies are necessary, but they must be done without delaying or interrupting steroid therapy, which often must be administered immediately to avoid serious vascular accidents, as mentioned above. The patient to be reported here demonstrated this clinical point.

CASE REPORT

On Sept 16, 1987, a 71-year-old woman was seen in neurologic consultation because of increasingly severe occipitotemporal headache that had progressed over the preceding 3 months. In addition, she complained of severe hip and pelvic pain of 3 weeks' duration and had experienced intermittent bilateral visual loss for 2 weeks, noted when she was attempting to read newspapers.

Her husband stated that her voice had changed over the preceding week. He described it as high-pitched, breathless, and "baby-like." The patient had noted speech changes, which she ascribed to fatigue, and she also reported severe laryngeal pain during speaking as well as jaw claudication during chewing that began 3 days before her examination. The patient denied past functional illnesses, and her husband confirmed the fact that she had no neuroses or psychiatric history. She did have a past history of osteoarthritis and osteoporosis and reported she had had 17 vertebral fractures, treated with estrogen, calcium, and bed rest.

The neurologic examination revealed pain and edema to palpation alongside the larynx, pain over the superficial temporal and carotid arteries, pain over the lumbosacral joint, and changes in her speech. It was falsetto, with a breathy quality. In addition, there were downward pitch breaks with phonation breaks that occurred during portions of words, as well as for sentences. The overall quality of her speech was high-pitched and prepubescent, with a breathless and excited sound. Hoarseness was not present. Giant cell arteritis and polymyalgia rheumatica were suspected.

The patient was sent immediately for a measurement of Westergren ESR, which was 108 mm/h, and was admitted to The Medical Center of Delaware, where the ESR was tested again and found to be 135 mm/h. She was given a 100-mg dose of intravenous hydrocortisone sodium succinate, followed by oral prednisone, 80 mg/d in divided doses.

On the first day of admission, results of the rheumatoid factor test were negative, and of the antinuclear antibody quantitative test were less than 1:40. Osteoarthritis of the entire spine was seen on radiographs, but no osteoporosis was seen; and biopsy of the superficial temporal artery on the right revealed numerous inflammatory cells in all layers of the artery, and giant cells were not seen.

Her course was one of improvement in the following sequence after administration of the intravenous bolus of hydrocortisone: her visual blurring cleared almost immediately, her headache cleared after 1 hour, her voice became normal in 4 hours, and her ESR was found to be 35 mm/h at the next determination, 12 hours after admission (no serial ESRs were done; hence, the exact time of return to normal was not known). An examination of her nasopharynx and larynx was performed after her voice had returned to normal, and no abnormality was seen.

On the fourth hospital day after her steroid dosage had been decreased from 80 to 70 mg/d, she complained of severe headache and prostration, she lost central vision, and her voice again became abnormal, as it was before admission. An emergency ESR test yielded an ESR of 117 mm/h; at this time the patient was given an additional bolus of 200 mg of intravenous hydrocortisone sodium succinate. Her vision returned to normal in 1 hour and her headache cleared in 4 hours, at which time she began to speak normally again. Upon discharge, her daily maintenance dose of prednisone was 75 mg/d. During follow-up, her dose has been 25 mg/d, and she has been free of the above-mentioned signs and symptoms.

DISCUSSION

The signs and symptoms of giant cell arteritis are so numerous and the anatomy and physiology of speech are so complex that one must expect the differential diagnosis to include a myriad of diseases. These include: functional diseases; CNS lesions, including vascular ones; neuromuscular diseases, including neuropathies; diseases of the respiratory tree and larynx, including ischemia, inflammation, and orthopedic disorders; rheumatic dislocation of cricoarytenoid joints; Wegener's granulomatosis; relapsing polychondritis; and also metabolic disorders such as thyroid and adrenal disease.[13-15,19-26]

Included in the above are four diseases that often mimic giant cell arteritis, because the ESR usually is elevated and the respiratory system can be involved: disseminated lupus, rheumatoid dislocation of the cricoarytenoid joint, Wegener's granulomatosis, and relapsing polychondritis.[24-26] In considering the myriad of diagnoses suggested above, it is interesting to note the two diverse but related causes of speech and respiratory disorders suggested by the authors of three articles.[1,6,7] Dresser[1] speculated that there was ischemia from large vessels and mucosal damage from small ones. A similar vascular mechanism was proposed by Larson et al,[6] who also mentioned lesions of the bronchial mucosa from occlusion of branches of the aorta. On the other hand, Jennings[7] discovered edema and round cell infiltration in a biopsy of laryngeal mucosa in an elderly man with giant cell arteritis.

Even though ischemic lesions of the central and peripheral nervous systems occur in 5% to 15% of patients with this disease,[13-15] it is surprising that cerebrovascular occlusive disease has not been proposed to explain respiratory symptoms and speech disturbances. Other symptoms produced by nervous system ischemia have been hallucinations, syncope, seizures, stroke, deafness, ataxia, myeloradiculopathy, and peripheral neuropathy.[13-15] Aphasias were not listed separately from "stroke"; hence, central speech disturbances probably have been underreported. There is only an indirect nervous system relationship mentioned in the work of Dresser,[1] the author who first described voice changes, and who in the same paper mentioned miosis due to ischemia of the superior cervical sympathetic ganglion.

Patients with giant cell arteritis are usually acutely and chronically ill, and appear to the physician to be toxic, debilitated, and depressed. Because almost every system is involved, the patients have fever, sweats, anorexia, weight loss, malaise, headache, myalgia, and arthralgia. In this setting, one might expect a large number of functional speech disturbances.[19] It is interesting that thus far, no author (who has described vocal or respiratory changes in patients with vasculitis) has suggested hysteria or neurosis as a cause. Greene[20] has described the clinical characteristics of dysphonias due to neurosis, which occur more often in women than in men. The basic understanding of functional speech disorders, however, came from the work of

Smurthwaite[27] and Moses,[28] who studied combat dysphonias in soldiers from two wars. The above authors described the following laryngoscopic findings: ease of manipulation of the vocal cords, which lie laterally; lack of adduction with defects of cord apposition; and obliteration of the laryngeal ventricle of Morgagni by cord spasm.

The patient reported here had no history of psychiatric illness or depression, and she had a rapid response to steroid therapy during two separate episodes, which suggested that her disease was organic and not functional. The quality of her speech resembled a type of spastic dysphonia, which usually is produced by tight laryngeal adduction.[19,29] Unfortunately, the rapid course of her illness precluded the performance of laryngoscopy while she was symptomatic in order to prove or disprove this thesis. Even though spastic dysphonias usually are listed under functional disorders, Moore et al[19] and Boone and McFarlane[29] have reported that there is also a neurogenic cause, and surgery has been an effective treatment in over 300 patients.

A review of available literature, therefore, discloses three possible mechanisms for speech and respiratory disorders stemming from arteritis: large vessel disease, small arterial ischemia, and direct round cell and inflammatory invasion of the respiratory mucosa.[1,6,7] There are 11 extrinsic and seven intrinsic muscles of the larynx; four of the latter adduct the vocal cords so that they can allow the cords to vibrate by the passage of air over them during speaking, after being forced apart by respiratory pressure. This necessitates long periods of contraction and high oxygen demand. Blood supply is through the superior and inferior laryngeal arteries, as well as the cricothyroid arteries. During ischemia (as from arteritis) muscle tissue shortens, the fibers swell, and pain results. This is the most likely mechanism to explain the present patient's voice changes, and also will explain her rapid and dramatic improvement on two occasions 4 hours after she received intravenous steroid therapy.

REFERENCES

1. Dresser EJ. Miosis, trismus, and dysphagia. An unusual presentation of temporal arteritis. Ann Intern Med 1969;71:961-2.

2. Hutchinson J. Diseases of the arteries. On a peculiar form of thrombotic arteries of the aged which is sometimes productive of gangrene. Arch Surg (Lond) 1890;1:323-9.

3. Horton BT, Magath TB, Brown GE. An undescribed form of arteritis of the temporal vessels. Mayo Clin Proc 1932;7:700-1.

4. Hamilton CR Jr, Shelley WM, Tumulty PA. Giant cell arteritis: including temporal arteritis and polymyalgia rheumatica. Medicine (Baltimore) 1971;50:1-27.

5. Kelly WN, Harris ED Jr, Ruddy S, Sledge CB. Textbook of rheumatology. Philadelphia: WB Saunders, 1985:524-5, 1166-73.

6. Larson TS, Hall S, Hepper NGG, Hunter GG. Respiratory tract symptoms as a clue to giant cell arteritis. Ann Intern Med 1984;101:594-7.

7. Jennings GH. Uncommon disease onsets with dysphagia. Practitioner 1969;202:808-15.

8. Gilmour JR. Giant-cell chronic arteritis. J Pathol Bacteriol 1941;53:263-77.

9. Paulley JW, Hughes JP. Giant-cell arteritis, or arteritis of the aged. Br Med J 1960;2:1562-7.

10. Fauchald P, Rygvold O, Oystese B. Temporal arteritis and polymyalgia rheumatica, clinical and biopsy findings. Ann Intern Med 1972;77:845-52.

11. Huston KA, Hunder GG, Lie JT, Kennedy RH, Elveback LR. Temporal arteritis: a 25-year epidemiologic, clinical and pathologic study. Ann Intern Med 1978;88:162-7.

12. Kansu T, Corbett JJ, Savino P, Schatz NJ. Giant cell arteritis with normal sedimentation rate. Arch Neurol 1977;34:624-5.

13. Calamia KT, Hunder GG. Clinical manifestations of giant cell (temporal) arteritis. Clin Rheumat Dis 1980;6:389-403.

14. Moore PM, Cupps TR. Neurological complications of vasculitis. Ann Neurol 1983;14:155-67.

15. Wong RL, Korn JH. Temporal arteritis without an elevated erythrocyte sedimentation rate. Case report and review of the literature. Am J Med 1986;80:959-64.

16. Allsop CJ, Gallagher PJ. Temporal artery biopsy in giant cell arteritis. A reappraisal. Am J Surg Pathol 1981;5:317-23.

17. Hall S, Persellin S, Lie JT, O'Brien PC, Kurland LT, Hunder GG. The therapeutic impact of temporal artery biopsy. Lancet 1983;ii:1217-20.

18. Temporal artery biopsy [Editorial]. Lancet 1983;i:396-7.

19. Moore GP, Hicks DM, Abbott TB. Defects of speech and language. In: Ballenger JJ, ed. Diseases of the nose, throat, ear, head and neck. Philadelphia: Lea & Febiger, 1985:692-731.

20. Greene MCL. The voice and its disorders. Philadelphia: JB Lippincott, 1972:1-31.

21. Negus VE, Fry DB. Voice. In: Dodge JV, ed. Encyclopaedia Britannica. 32nd ed. Chicago: William Benton, 1964;23:223-38.

22. Ballenger JJ. Diseases of the nose, throat, ear, head and neck. Philadelphia: Lea & Febiger, 1985:376-85.

23. Spector GJ, Ogura JH. Tumors of the larynx and laryngopharynx. In: Ballenger JJ, ed. Diseases of the nose, throat, ear, head and neck. Philadelphia: Lea & Febiger, 1985:549-602.

24. Weiser GA, Forouhar FA, White WB. Hydralazine hoarseness, a new appearance of drug-induced systemic lupus erythematosus. Arch Intern Med 1984;144:2271-2.

25. Hart ED. Complicated rheumatoid disease. Br Med J 1966;2:131-5.

26. Djalilian M, McDonald TJ, Devine KD, Weiland LH. Nontraumatic, nonneoplastic subglottic stenosis. Ann Otol Rhinol Laryngol 1975;84:757-63.

27. Smurthwaite H. War neurosis of the larynx and speech mechanism. J Laryngol Otol 1919;34:13-20.

28. Moses PJ. The voice of neurosis. New York: Grune and Stratton, 1954.

29. Boone DR, McFarlane SC. The voice and voice therapy. 4th ed. Englewood Cliffs, NJ: Prentice Hall, 1988:56-7.

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PROGRESSIVE HEARING LOSS IN USHER'S SYNDROME

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In 18 patients with Usher's syndrome, progressive hearing loss was verified audiologically in eight cases. Despite poor auditory threshold values and low speech discrimination scores, there was only one patient who could not communicate with speech. The possibility of hearing impairment being mainly progressive in Usher's syndrome is discussed.

KEY WORDS — progressive hearing loss, Usher's syndrome.

INTRODUCTION

Usher's syndrome is the leading disorder of combined deafness and blindness after childhood.[1] The main characteristics of Usher's syndrome are congenital hearing loss and retinitis pigmentosa. Mental disturbances and vestibular dysfunction are also, in some cases, parts of the disease picture. The disorder affects some 3/100,000 people in the general population, but the prevalence of Usher's syndrome among the congenitally deaf is estimated to be between 3% and 6%.[2]

At present Usher's syndrome is classified on the basis of various phenotypic manifestations (types 1, 2, and 3) and inheritance patterns (type 4).[3] Usher's syndrome type 3 is characterized by progressive hearing loss. The results of vestibular examinations also have been used to differentiate various types of Usher's syndrome.[4]

The hearing loss is bilateral and generally is accepted to be cochlear in origin.[5-9] Deafness usually is reported to be present at birth, and usually is so severe in early childhood that rehabilitative measures are needed. However, total deafness is very rare, and hearing loss usually is discovered early in childhood. There may have been some previous deterioration, but actual hearing abilities during the first years of life have remained obscure. Some believe the loss to remain constant or to progress slightly with age.[1] It also has been reported that children affected within a given family tend to exhibit a significant positive family correlation with respect to level and pattern of hearing impairment.[1,9,10] However, most of these studies are based on the reported observations of patients or their families, not upon longitudinal audiometry.

Patients with Usher's syndrome living in the province of Kuopio are examined and followed up at Kuopio University Central Hospital, and in many patients progression of the disease has been monitored over a period of 20 years (Table 1). We present the audiologic findings of 18 patients that suggest that progressive hearing impairment is a common manifestation of Usher's syndrome, at least in eastern Finland.

MATERIAL AND METHODS

The material consisted of 18 patients from the province of Kuopio, all of whom had audiologically and ophthalmologically verified Usher's syndrome. The patients came from 12 families. Patients 1, 2, 12, and 16 were siblings. The sister (patient 18) of patient 6 last underwent audiologic measurements in 1979 and has since refused further examinations. Patients 3, 13, and 15 were also siblings, and had another affected sister who was not examined by us. Patient 11 had two siblings also suffering from Usher's syndrome, but neither was examined by us. According to the family history, the brother (47 years of age) was speechless and had poor visual acuity, and the sister (44 years of age) had visual and hearing losses but was able to speak.

Nine of the patients were male, with a mean age of 44 years (range, 15 to 61 years), and nine were female, with a mean age of 34.1 years (range, 14 to 53 years). Case histories covered ear diseases, anamnestic hearing impairment and visual loss, and education. All patients had undergone audiologic examination many times during the follow-up period, and the most typical audiograms were selected for presentation (Table 1). The patients also had under-

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TABLE 1. AUDIOMETRICALLY VERIFIED PROGRESSIVE HEARING LOSS

				Pure Tone Threshold in Right Ear (dB)				*Pure Tone Threshold in Left Ear (dB)*				
Patient	*Age**	*Sex*	*Audiogram Date*	*250 Hz*	*500 Hz*	*1,000 Hz*	*2,000 Hz*	*250 Hz*	*500 Hz*	*1,000 Hz*	*2,000 Hz*	*Speech Discrimination Scores, Right/Left (%)*
1	51	F	1967	45	50	90	85	55	60	85	80	40/50
			1975	40	55	90	95	50	60	85	95	
			1982	50	65	100	115	55	70	90	115	0/0
2	47	F	1981	35	40	45	65	25	35	55	55	60/90
			1986	50	60	70	70	50	60	75	80	0/84
3	32	M	1962	35	45	60	60	35	40	50	60	
			1971	50	55	65	70	40	50	55	60	
			1985	60	70	80	75	60	70	70	70	70/90
4	31	F	1963	55	65	90	80	85	95	95	90	
			1977	90	100	100	110	105	95	110	95	
			1984	95	100	100	110	105	95	110	115	0/0
5	27	M	1968	15	20	25	35	10	20	30	35	
			1979	45	60	70	65	40	50	65	65	
			1986	50	60	80	70	60	65	80	70	76/84
6	24	F	1978	25	35	35	40	25	30	40	40	
			1986	45	45	55	55	50	45	50	55	88/92
7	17	F	1973	50	60	65	65	55	65	60	65	
			1981	45	70	90	85	60	70	80	65	0/57
			1985	80	100	110	120	110	115	115	120	0/0
8	15	M	1978	60	55	65	50	65	70	60	55	75/67
			1979	65	70	75	70	65	70	85	80	
			1986	75	80	95	100	85	85	100	95	50/67

*At time of last hearing examination.

gone routine ophthalmologic examinations, together with manual or automatic perimetry whenever possible. In some instances electrophysiologic examinations such as electroretinogram and visual evoked potential were included. The results of these examinations are given below. Hearing threshold levels are presented according to the standard reference zero for the calibration of audiometers (ISO/R 389-1964). Bisyllabic phonetically balanced Finnish taped word lists[11,12] have been used for speech discrimination tests. The speech ability of patients was evaluated according to how well speech could be understood. The classification "mild speech disorder" was used if there was only a slight speech disorder. The typical speech disorder connected with profound hearing impairment was termed "moderate speech disorder," but speech was still easy to understand, and these patients used it to communicate.

RESULTS

Normal tympanic membranes were found in all cases. Progressive hearing loss was verified audiologically in eight patients (Table 1). All patients with audiologically proven progressive hearing loss had measurable threshold values at speech frequencies and also exhibited correct or intelligible speech and language (patients 1 through 8; Table 2). With the exception of patient 8, all had passed through primary school, and some even through secondary school.

Anamnestic histories revealed considerable differences among the subjects in the age at which hearing impairment and visual loss became manifest. Clear differences also were observed among siblings, eg, among patients 1, 2, 12, and 16 (sisters) (Tables 2 and 3) (earlier reported by Karjalainen et al[13]). Patient 2 had become aware of hearing impairment at age 30, and her hearing was clearly better than that of her siblings. Clear differences in manifestation of the disease also were observed among patients 3, 13, and 15 (brothers).

Of the remaining eight patients (Table 2; patients 9, 10, 11, 12, and 16), five had experienced progressive hearing loss since childhood. Only one patient (patient 14) was unable to communicate verbally. After starting at a normal school, she had switched to a special school for the deaf.

DISCUSSION

The progressive type of Usher's syndrome is described in the literature as rare.[3,9,14] Nuutila[10] reported progressive hearing loss in only four of 138 patients (3%) in Finland. However, Merin et al[15] reported slowly progressive hearing loss in nine of 35 patients (26%) suffering from Usher's syndrome. Objective audiologic follow-up measurements in the present study indicate that progressive hearing impairment associated with Usher's syndrome is also common, at least in the eastern part of Finland. Discrepancies between speech acuity and hearing levels (Table 3) suggest that hearing levels were bet-

TABLE 2. CASE HISTORIES OF HEARING IMPAIRMENT, AUDIOMETRIC FINDINGS AT LAST FOLLOW-UP EXAMINATION, SPEECH DEVELOPMENT, AND SCHOOLING

Patient	*Age**	*Sex*	*Anamnestic Age of Hearing Impairment*	*Speech Reception Thresholds, Right/Left (dB)*	*Speech Discrimination Scores, Right/Left (%)*	*Speech*	*School*
1	51	F	Adulthood	—/—	0/0	Mild SD	Primary
2	47	F	Age 30	60/65	0/84	Correct	Secondary
3	32	M	Mild congenital	70/65	70/90	Moderate SD	Primary
4	31	F	Mild congenital	—/—	0/0	Mild SD	Secondary
5	27	M	Mild congenital	70/60	76/84	Correct	Primary
6	24	F	Childhood	55/50	88/92	Correct	Secondary
7	17	F	Mild congenital	—/—	0/0	Moderate SD	Primary
8	15	M	Congenital	90/100	50/67	Moderate SD	SF deaf
9	61	M	Childhood	80/—	86/0	Correct	Primary
10	58	M	Age 7	65/65	100/100	Correct	Primary
11	56	M	Childhood	—/—	0/0	Moderate SD	Primary
12	53	F	Age 30	90/85	0/50	Correct	Primary
13	43	M	Congenital	—/—	0/0	Moderate SD	SF deaf
14	40	F	Congenital	—/—	0/0	No speech	SF deaf
15	39	M	Childhood	65/65	100/100	Correct	Primary
16	38	F	Congenital	—/—	0/0	Moderate SD	SF deaf
17	61	M	Adulthood	100/75	68/68	Mild SD	Primary
18	14	F	Childhood	20/25	93/100	Correct	Primary

SD — speech disorder, SF deaf — school for deaf. Dashes indicate no speech discrimination.

*At time of last hearing examination.

ter at some stage before diagnosis, even in those cases in which no audiologically verified progressive hearing loss has been observed. Kumar et al[4] observed significant differences in speech discrimination scores between patients with similar audiometric configurations and nearly identical pure tone averages, and suspected that this might also be a sign of progressive hearing impairment. Karp and Santore[16] presented audiologic findings and case reports of four of 25 patients who noted progressive sensorineural hearing loss concomitantly with the first visual symptoms. Also, Vernon's[2] findings raise the possibility that deafness and vestibular disease may be not only progressive, but also well advanced, by 2 or 3 years of age.

Patients in this study with audiologically proven progressive hearing loss generally showed better pure tone values and discrimination scores than the others (Table 2). This may result from the fact that patients 1 through 8 had milder hearing loss soon after birth, with later onset of hearing deterioration. Suspicion of hearing impairment often arises when a child is 1 to 2 years of age and shows delayed speech development. In such young children it is often impossible to measure hearing threshold values accurately, and even more difficult to ascertain whether hearing impairment is congenital. Thus the exact time of onset or the rapidity of deterioration of hearing impairment usually is not known, whereas the onset of visual impairment can be estimated more accurately (Table 3) and generally is known to be progressive.

In this study, progressive hearing loss was clearly the commonest form of hearing impairment associated with Usher's syndrome in the province of Kuopio. However, these patients represent only a small proportion of the estimated 300 to 400 people in Finland affected with Usher's syndrome. A more extensive study covering the entire country currently is being planned, and it remains to be seen whether the type distribution of Usher's syndrome in eastern Finland differs from that in other parts of the country. This may well be the case, since the

TABLE 3. VISUAL AND FAMILY HISTORIES

Patient	*Anamnestic Age of Visual Impairment*	*Last Ophthalmologic Examination*				*Others in Family With Usher's Syndrome*
		Year	*Age**	*RE*	*LE*	
1	Age 10	1982	51	CF	CF	3 sisters
2	Age 20	1982	43	LP	LP	3 sisters
3	Childhood	1981	28	8/20	8/20	2 brothers, 1 sister
4	Childhood	1986	33	6/20	6/20	Not known
5	Age 4	1984	25	6/20	6/20	Not known
6	Childhood	1986	24	6/20	5/20	1 sister
7	Age 17	1986	18	10/20	10/20	Not known
8	Age 14	1985	14	12/20	12/20	Not known
9	Childhood	1985	61	LP	LP	Not known
10	Late teens	1985	58	LP	LP	Not known
11	Teens	1979	50	CF	CF	1 brother, 1 sister
12	Age 30	1982	53	LP	NLP	3 sisters
13	Teens	1985	43	12/20	12/20	2 brothers, 1 sister
14	Adulthood	1985	40	7/20	7/20	Not known
15	Teens	1985	39	10/20	10/20	2 brothers, 1 sister
16	Teens	1985	38	LP	LP	3 sisters
17	Age 17	1981	56	LP	LP	Not known
18	Adulthood	1986	21	14/20	10/20	1 sister

RE — right eye, LE — left eye, CF — counting fingers, LP — light projection, NLP — no light projection.

*At time of last ophthalmologic examination.

population in eastern Finland is rather isolated and has remained within the same area for a long period of time.

Progressive hearing loss appears to differ a great deal among individuals, even within the same family. One of the sibships included in this study (patients 1, 2, 12, and 16) had been reported earlier[13] as having notably different ages of manifestation of both visual and hearing loss. We also know another family with four affected children who again show a wide variation in the age of manifestation.

Usher's syndrome was regarded earlier as a single, uniform disease, but currently is classified into four subtypes. However, the fact that progressive hearing loss seemed so common in this study, and that two families in our district did not fit the present classification, suggests that this classification is not valid for this particular geographic area. Considering the wide variation in visual acuity in this series of patients, we believe it is feasible to assume that the variance of phenotypes shown by audiologic status also applies to ophthalmologic manifestations of Usher's syndrome.

The advanced screening methods and objective hearing examinations (auditory brain stem response and stapedial reflex examination) of modern audiology facilitate audiologic examinations in young children. Monitoring hearing development in younger siblings of Usher's syndrome patients may make it possible in the future to evaluate whether a given type of Usher's syndrome is progressive in most or even all affected patients.

REFERENCES

1. Regenbogen L, Coscas G. Usher syndrome. In: Oculo-auditory syndromes. New York: Masson Publishing, 1985:290-5.

2. Vernon M. Usher's syndrome — deafness and progressive blindness: clinical cases, prevention, theory, and literature survey. J Chronic Dis 1969;22:133-51.

3. Gorlin RJ, Tilsner TJ, Feinstein S, Duvall AJ. Usher's syndrome type III. Arch Otolaryngol 1979;105:353-4.

4. Kumar A, Fishman G, Torok N. Vestibular and auditory function in Usher's syndrome. Ann Otol Rhinol Laryngol 1984; 93:600-8.

5. McLeod AC, McConnell FE, Sweeney A, Cooper MC, Nance WE. Clinical variation in Usher's syndrome. Arch Otolaryngol 1971;94:321-34.

6. Belal A Jr. Usher's syndrome (retinitis pigmentosa and deafness). A temporal bone report. J Laryngol Otol 1975;89: 175-81.

7. Abraham FA, Cohen D, Sohmer H. Usher's syndrome: electrophysiological tests of the visual and auditory systems. Doc Ophthalmol 1977;44:435-44.

8. Proctor C. Diagnosis, prevention and treatment of hereditary sensorineural hearing loss. Laryngoscope 1977;87(suppl 7).

9. Davenport SL, Omen GS. The heterogeneity of Usher's syndrome. Presented at the Fifth International Conference on Birth Defects, Montreal, Aug 21-27, 1977.

10. Nuutila A. Dystrophia retinae pigmentosa-dysacusis syndrome (DRD): a study of the Usher or Hallgren syndrome. J Genet Hum 1970;18:57-88.

11. Palva T. Finnish speech audiometry. Acta Otolaryngol [Suppl] (Stockh) 1952(suppl 101).

12. Jauhiainen T. An experimental study of the auditory perception of isolated bi-syllable Finnish words [Dissertation]. University of Helsinki, 1974.

13. Karjalainen S, Teräsvirta M, Kärjä J, Kääriäinen H. An unusual otological manifestion of Usher's syndrome in four siblings. Clin Genet 1983;24:273-9.

14. Beatty CW, McDonald TJ, Colvard DM. Usher's syndrome with unusual otologic manifestation. Mayo Clin Proc 1979;54:543-6.

15. Merin S, Abraham FA, Auerbach E. Usher's and Hallgren's syndromes. Acta Genet Med Gemellol (Roma) 1974;23:49-55.

16. Karp A, Santore F. Retinitis pigmentosa and progressive hearing loss. J Speech Hear Disord 1983;48:308-14.

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THE INTERNATIONAL SYMPOSIUM ON CLINICAL AND BASIC OTOLOGY

The International Symposium on Clinical and Basic Otology will be held June 4-6, 1990, in Beijing, People's Republic of China. The abstract deadline is December 31, 1989. For further information, contact the Beijing Institute of Otorhinolaryngology, Chan Liu, MD, Professor and Director, 17 Hougou Lane, Beijing 1000005, People's Republic of China.

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TREATMENT OF DEPRESSED TINNITUS PATIENTS WITH NORTRIPTYLINE

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Patients disabled by tinnitus show a high prevalence of major depression. Furthermore, tinnitus produces patterns of disability similar to those produced by major depression. To explore further this link between tinnitus and depression, and to investigate the efficacy of treating depression in the treatment of tinnitus, a single-blind, placebo-washout, nonrandomized pilot study of the tricyclic antidepressant nortriptyline (hydrochloride) was undertaken in disabled tinnitus patients who also met diagnostic criteria for major depression. Nineteen patients began the study, two responded to placebo, and two dropped out prior to completion. Fourteen considered their tinnitus improved, and 12 chose to continue taking nortriptyline after the study. Depression severity decreased, on the average, by 65% ($p < .0001$). Tinnitus loudness measured by audiometric matching decreased by a mean of 10 dB or 50% ($p < .02$). Self-reports of tinnitus loudness and severity, somatic and psychologic symptoms, and psychosocial dysfunction all showed significant improvement with treatment. These results suggest that what initially appears to be an irreversible otologic disability in these patients may be in large part a reversible psychiatric disability.

KEY WORDS — depression, tinnitus, tricyclic antidepressant.

INTRODUCTION

There is general agreement among otolaryngologists that therapeutic success is achieved in only a small minority of patients suffering from chronic tinnitus. There are a few well-known reversible causes for tinnitus (eg, drugs, neoplasm, vascular abnormality, Meniere's disease), but these represent less than 5% of those presenting with tinnitus as a chief complaint. When the degree of hearing loss warrants the use of a hearing aid, this often will improve the patient's tinnitus, supposedly by masking the tinnitus with outside sounds. Tinnitus maskers, which produce narrowband noise to mask tinnitus, have proved disappointing in most clinics. Only 50% of patients will buy a recommended masker, and only 11% will continue to wear the masker at 6 months.[1] Biofeedback, relaxation, and stress reduction programs have been used widely.[2] The only well-controlled study in this area, however, was unable to demonstrate decreases in tinnitus sensation or disability.[3]

Many medications have been proposed for tinnitus control. Intravenous lidocaine hydrochloride has been significantly better than placebo in three of four randomized clinical trials (eg, Hulshof and Vermeij[4]), but its clinical use is impractical. Its oral analog, tocainide (hydrochloride), has been successful in open trials, but has not been more successful than placebo in studies with double-blind controls.[5] Similarly, carbamazepine has not shown significant benefit when compared to placebo.[6] Cochlear nerve section, generally done only in those who are already deaf, is agreed by most otologists to be of little if any lasting benefit.

Prevalence estimates from epidemiologic community surveys suggest that approximately 15% of the general population experiences frequent or constant tinnitus that is not induced temporarily by noise.[7-9] Hearing threshold has been reported as the primary risk factor determining the prevalence of tinnitus.[10] As hearing threshold increases, generally because of age or noise exposure, there is an exponential increase in the number of tinnitus cases.

While the risk of developing tinnitus is directly proportional to one's degree of sensorineural hearing loss, tinnitus severity does not show a clear correlation with degree of hearing loss.[10] British surveys[7,11] have found that only 14% of tinnitus sufferers experience "severe annoyance" and only 4% experience severe disability due to their tinnitus. Similar results have been obtained in Sweden.[9] Though frequency and length of tinnitus episodes correlated with severity, only one third of those experiencing continuous tinnitus reported it as severe. Indeed, the vast majority of those with tinnitus never seek medical attention for it. Ninety-five percent of those that consult their physician are satisfied with reassurance that their tinnitus is not a symptom of a serious, progressive disease.[7]

If tinnitus is a benign, albeit temporarily worrisome sensation for most persons, what distinguishes severe and disabling tinnitus from the more common benign form? House et al[2] found no difference in tinnitus loudness (estimated by comparison to externally presented tones) between those who were disturbed by their tinnitus and those who were not. Meikle et al[12] showed that there was no correlation between the self-rated severity of tinnitus and its

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TABLE 1. DSM-III-R CRITERIA FOR MAJOR DEPRESSION

A. A predominant and persistent dysphoric mood most of the day, nearly every day for at least two weeks:
   1. Feeling sad, blue, or depressed, or
   2. Loss of interest or pleasure in usual activities

B. And, four of eight symptoms listed below, nearly every day for at least a two-week period:
   1. Poor appetite or significant weight loss, increased appetite or significant weight gain.
   2. Insomnia or hypersomnia.
   3. Psychomotor retardation or agitation.
   4. Loss of interest or pleasure in usual activities.
   5. Loss of energy; fatigue.
   6. Feelings of worthlessness, excessive or inappropriate guilt.
   7. Diminished concentration, or indecisiveness.
   8. Recurrent thoughts of death, wishes to be dead, or suicidal thoughts.

C. Not the consequence of an uncomplicated bereavement or organic mental disorder.

From the *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed, rev. American Psychiatric Association, 1987.

measured loudness, pitch, or constancy. Only a slight correlation was found between severity and duration, tonal quality, maskability, or number of sounds comprising the tinnitus. Severity correlated best with decreased concentration, disrupted social relations, and disturbed sleep. These results suggest that tinnitus severity is tied more closely to the degree of psychosocial disruption than to intrinsic properties of the noise sensation. It is suggested by the type of disability reported by tinnitus sufferers that depression may distinguish those disabled by their tinnitus from those who are not disabled.

Tinnitus long has been described as being exacerbated by psychosocial stressors and as being a significant source of distress.[13] The prevalence of psychopathology in tinnitus sufferers has been described anecdotally[14] in the otolaryngologic literature. Multiple studies[15-17] have found elevated scores for anxiety and depression in tinnitus patients on self-report measures such as the Minnesota Multiphasic Personality Inventory.

These past studies suffered from methodologic flaws such as 1) biased sampling from a tinnitus subgroup selected for psychologic treatment, 2) the lack of an adequate control group, 3) the lack of operationalized diagnostic criteria for psychiatric illness, and 4) mixing of tinnitus patients with minimal and severe disability. We therefore carried out a study[18] to assess the prevalence of psychiatric illness in patients attending a Tinnitus Research Clinic as compared to a control group complaining of hearing loss using the National Institute of Mental Health Diagnostic Interview Schedule (NIMH-DIS) structured psychiatric interview. We also used self-report questionnaires to assess psychosocial disability in depressed and nondepressed tinnitus patients as compared to the controls. Two main conclusions resulted from this study. First, tinnitus patients have a much higher prevalence of both current (60% versus 7%, $p<.001$) and lifetime (78% versus 21%, $p<.002$) major depression as defined in the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-III) (refer to Table 1 for diagnostic criteria) than hearing loss controls. Second, disability due to tinnitus has a strong association with affective disorder; nondepressed tinnitus patients were not significantly different from controls on any of the disability measures, while depressed tinnitus patients were significantly more disabled on all measures used than both controls and the nondepressed group. These results suggest that what initially appears to be an irreversible otologic disability in these patients may be in large part a reversible psychiatric disability.

There are anecdotal reports (eg, Goodey[19]) and a very recent double-blind study[20] of the use of tricyclic antidepressants in the treatment of tinnitus. This recent study, which found no therapeutic benefit from trimipramine maleate, has three serious flaws, however. First, the psychiatric status of their patients, including diagnosis, was not determined adequately (most were apparently not depressed). Second, the degree of disability due to tinnitus suffered by these patients was not specified. Third, this study did not distinguish outcome in terms of effect upon loudness or effects upon disability. Any or all of these factors could have obscured a significant treatment effect.

Our previous work cited above indicates that disability due to tinnitus may be strongly related to concurrent (DSM-III) major depression. To further investigate the role of depression in tinnitus disability and, specifically, to determine if reduction in depression severity can reduce tinnitus disability, we performed a single-blind, placebo-washout, nonrandomized pilot study treating chronic tinnitus patients with major depression using nortriptyline (hydrochloride). This design permits an economical determination of whether the considerable expense of a fully randomized clinical trial is justified. This type of design is especially appropriate for the preliminary study of tricyclic antidepressants, which require both dose adjustment and prolonged treatment for maximum therapeutic effect.

MATERIALS AND METHODS

Patients were referred from local otolaryngologists for treatment at our Tinnitus Research Clinic or recruited from a newspaper advertisement asking for people suffering from tinnitus and depression. All new patients in this Clinic received complete otologic and audiologic examinations, the latter including tinnitus matching and masking evaluation using procedures recommended by the 1981 Symposium on Tinnitus. Following this evaluation, patients without an otologically treatable cause for their tinnitus received the NIMH-DIS[21] from a psychiatrist. Patients with current DSM-III major depression and a minimum score of 18 on the Hamil-

TABLE 2. POSTTRIAL TREATMENT SUMMARY

	No. of Patients Who Requested Hearing Aid or Masker	*No. of Patients Who Requested Psychotherapy*	*No. of Patients Who Requested No Additional Therapy*
Patients who continued nortriptyline	4	5	3
Patients who discontinued nortriptyline	1	2	4

ton Depression Rating Scale (HAM-D)[22] but no history of psychosis or mania and no active drug or alcohol abuse were eligible for entry into the study. All patients completed the Hopkins Symptoms Checklist-90 (SCL-90)[23] and the Chronic Illness Problem Inventory (CIPI)[24] at the beginning and end of the study. Adults from 18 to 75 years of age were accepted if they passed interview screening for glaucoma, urinary retention, seizure disorder, hyperthyroidism, hypothyroidism, and pregnancy. Patients were screened for active cardiovascular disease by history, physical examination, and ECG if over 40 years of age. Patients were excluded from the study if they were on medications known to cause depression, eg, lipophilic β-blockers, reserpine, or steroids.

Patients were informed they would receive placebo at some time during the trial; in fact, all patients received placebo for the first 2 weeks of treatment. The placebo was lactose in gelatin capsules, indistinguishable from our nortriptyline capsules. Patients took a single capsule at bedtime for 2 weeks. Patients were asked to keep a daily tinnitus diary recording duration, loudness, and severity of tinnitus. At the end of 2 weeks, response to placebo was assessed for both depression and tinnitus by use of the HAM-D and a tinnitus questionnaire that assessed loudness, duration, and severity of tinnitus. The primary dependent variable for data analysis was tinnitus severity. If either the HAM-D or tinnitus severity scores decreased by 30% or more, the patient was judged a placebo responder. Such patients then were treated with active medication according to study protocol.

After 2 weeks of placebo, nortriptyline hydrochloride was begun as a single 25-mg nightly dose and increased 25 mg at 5-day intervals if no significant benefits or serious side effects were noted. Patients continued with daily tinnitus diaries and biweekly HAM-D and tinnitus questionnaires. Patients' blood levels of drug were assessed at 75 or 100 mg at the discretion of the treating psychiatrist. The dose was titrated to therapeutic blood level (50 to 150 ng/mL), at which patients were maintained for 6 weeks. At the end of this period, the trial was over. Patients were assessed again with the SCL-90, the CIPI, tinnitus matching, and masking, in addition to the tinnitus questionnaire and HAM-D used throughout the study. Patient satisfaction with treatment was assessed at trial completion and again at 1-month follow-up.

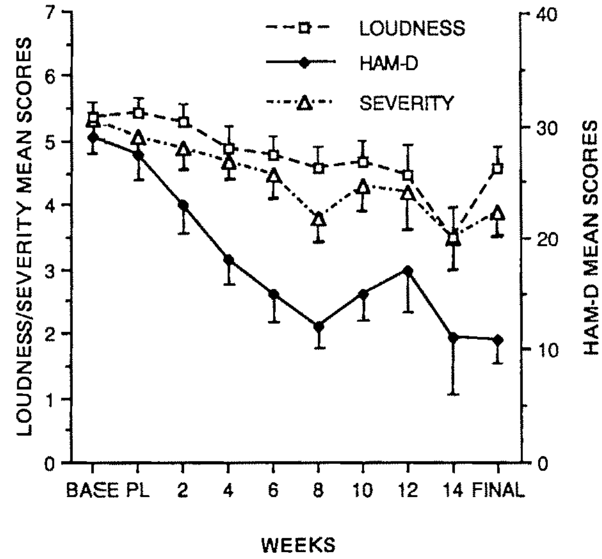

Fig 1. Treatment course with tinnitus measures scaled on left and depression measure on right (mean ± SEM). PL — postplacebo mean, HAM-D — Hamilton Depression Rating Scale. Patients were in trial for 10 to 14 weeks, depending upon how long titration of nortriptyline took.

RESULTS

Nineteen patients began the study. One patient's depression became worse, and he was referred for more intensive psychiatric treatment of paranoid symptoms after 12 weeks on the protocol. One patient discontinued the medication himself just prior to completion of the protocol. Data from both patients are included in the results. Most patients had minor side effects, including dry mouth, dyspepsia, constipation, and orthostatic hypotension. Two patients developed urinary hesitancy that required the addition of cholinergic medication. All patients were maintained at therapeutic blood levels for 6 weeks. Plateau doses ranged from 50 to 150 mg/d, with a median of 100 mg.

Fourteen patients considered their tinnitus improved at completion of the study, and five did not. Two of these responders also responded to placebo. No patients reported complete disappearance of their tinnitus with treatment, although two noted extended periods in which they had no tinnitus. Twelve patients continued nortriptyline treatment following completion of the study. Five of these 12 patients additionally sought psychotherapy. Five of the 19 study patients sought further treatment for their tinnitus in the form of a hearing aid or masker at the 1-month follow-up visit (Table 2).

Depression severity was monitored pretreatment, biweekly during treatment, and with the HAM-D posttreatment. Figure 1 shows the course of mean HAM-D scores. Pretreatment scores were not sig-

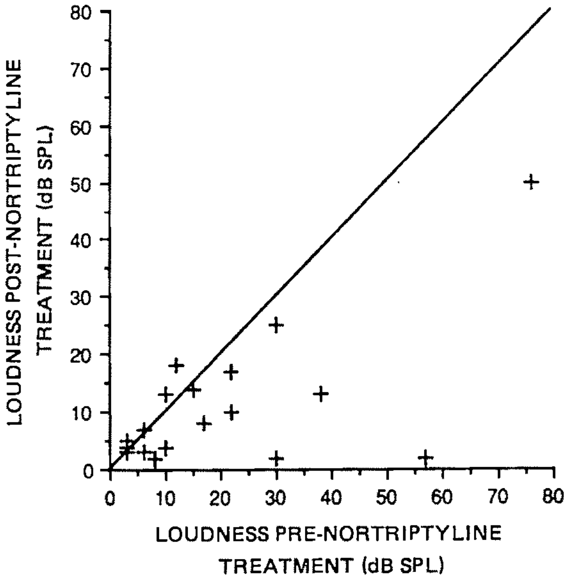

Fig 2. Pretreatment and posttreatment tinnitus loudness matches in worse ear. Line designating pretreatment and posttreatment equivalence is included for comparison.

nificantly different from scores after 2 weeks of placebo treatment. Pretreatment and postplacebo means were significantly greater than posttreatment scores ($p < .0001$) on two-tailed paired *t* tests. The mean decrease in HAM-D scores was 63%.

Tinnitus loudness in the patient's worse ear, as measured by matching with a tone of the same frequency in the ipsilateral ear, was significantly decreased ($p < .02$) after treatment. The mean decrease was 10 dB sound pressure level (SPL) or 50%. The decrease was most marked in those whose initial tinnitus-match loudness was greater than 20 dB SPL (Fig 2). The matching frequency often also changed with treatment, though this change had no discernible pattern.

Tinnitus loudness and tinnitus severity as assessed by biweekly audiologist interviews both were decreased significantly posttreatment ($p < .01$). The mean tinnitus severity decrease was 27%, while loudness decreased a mean of 15%. Loudness and severity also were decreased significantly posttreatment, as measured by self-report in daily diaries ($p < .05$). Pretreatment and postplacebo means were not significantly different. Figure 1 describes the course of change in tinnitus loudness and severity as compared to the change in depression severity.

Changes in somatic and psychologic symptoms with treatment were monitored on the SCL-90 (Fig 3). Seventeen patients completed the SCL-90 pretreatment and posttreatment. Scores on all scales were reduced significantly with treatment ($p < .01$), except somatic symptoms, which did not achieve statistical significance, and phobic avoidance, which achieved significance at the .05 level.

Psychosocial dysfunction was monitored with the CIPI (Fig 4). Problems in the areas of sexual functioning, physical appearance, physical activity, social activity, financial concerns, and illness focus were reduced ($p < .05$). Significant reductions also were noted in cognitive dysfunction ($p < .01$) and, even more clearly, in sleep disturbance and body deterioration ($p < .001$).

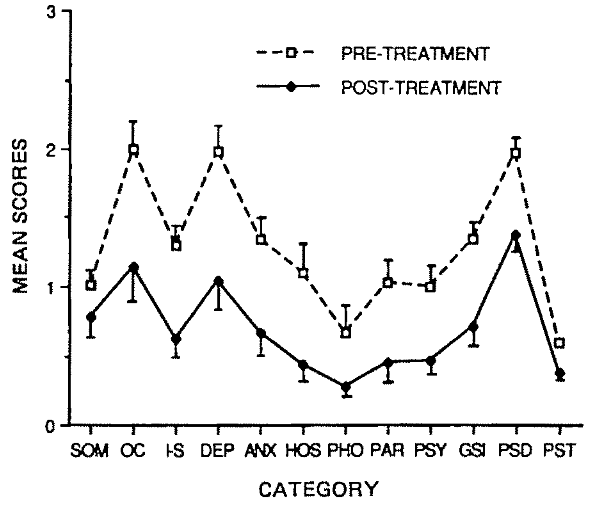

Fig 3. Pretreatment and posttreatment scaled mean scores ± SEM on Hopkins Symptoms Checklist-90. SOM — somatic focus, OC — obsessive/compulsive, I-S — interpersonal sensitivity, DEP — depression, ANX — anxiety, HOS — hostility, PHO — phobic avoidance, PAR — paranoia, PSY — psychosis, GSI — general symptom severity, PSD — psychopathic deviance, PST — psychasthenia/rumination.

DISCUSSION

This study demonstrates that patients with tinni-

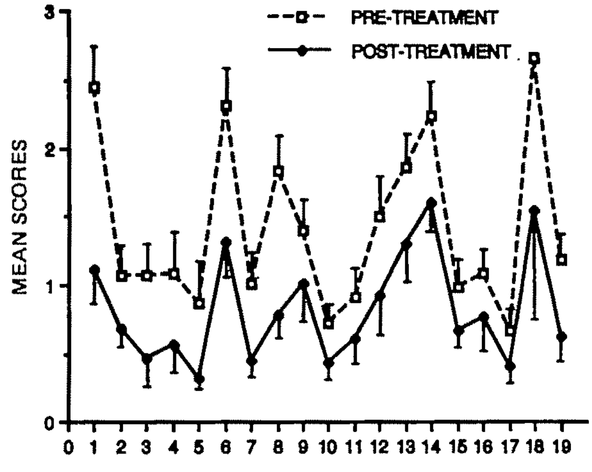

Fig 4. Chronic Illness Problem Inventory mean scores ± SEM pretreatment and posttreatment. For categories, 1 — sleep, 2 — eating, 3 — finances, 4 — employment, 5 — medications, 6 — cognitive, 7 — physical appearance, 8 — body deterioration, 9 — sex, 10 — activities of daily living, 11 — inactivity, 12 — social activity, 13 — family/friends contact, 14 — assertion, 15 — medical interaction, 16 — marital difficulty, 17 — marital overprotection, 18 — nonmarried relationships, 19 — illness focus. For scores, 0 — none, 1 — mild, 2 — moderate, 3 — severe.

tus who meet DSM-III criteria for major depression show significant improvement on a broad range of outcome measures when treated with the tricyclic antidepressant nortriptyline. There appears to be a hierarchy of response. The greatest improvement is seen in depression, psychologic and physical symptom severity, psychosocial disability, and global satisfaction. Less improvement is seen in tinnitus severity, and the least (although still significant) improvement is seen in tinnitus loudness as measured by audiometric matching and self-report.

Our study differs from previously reported studies[20] of tricyclic antidepressant treatment for tinnitus in that 1) only patients with current major depression were treated, 2) all patients had therapeutic tricyclic blood levels for 6 weeks, and 3) a broad array of audiometric and psychosocial outcome measures were used. Our ability to show treatment effect could be due to any of these reasons. In addition, some of our responders could be placebo responders who were not identified during the 2-week placebo washout period. We plan a double-blind, randomized trial to obtain a true placebo response rate.

Tinnitus can be conceptualized as having three components: 1) tissue injury (ie, to cochlear hair cells), 2) symptoms produced (ie, tinnitus noise of a given loudness, frequency, etc), and 3) disability experienced (eg, sleep disruption, marital discord). It is not likely that tricyclics act to reverse cochlear damage. However, there are grounds to believe that tricyclic treatment may reduce the production of symptoms from a given injury and/or the production of disability by a given set of symptoms.

The ability of tricyclic antidepressants to relieve depression in 60% to 70% of those who meet criteria for major depression is well documented and confirmed in the present study. It has been shown further in several studies that patients with major depression have significantly more somatic complaints of a nonspecific nature than control subjects who are not depressed.[25] In a study of patients with a variety of chronic medical illnesses,[26] it was found that depressive symptoms had large and significant effects upon perceived general as well as mental health status, and upon social, vocational, and physical functioning. More specifically, a recent study that compared 51 patients with major depression to 51 matched controls on the incidence and severity of 27 physical symptoms found that 49% of depressed patients complained of tinnitus, compared to 11.8% of controls.[25] Relieving depression in itself, therefore, should diminish somatic symptoms.

The most well-studied phenomena of medical-psychiatric comorbidity are those of chronic pain. Chronic tinnitus offers some intriguing parallels to chronic pain. Each has an important association with depression that appears to amplify symptoms of medical origin.[27] Each can occur following peripheral denervation (cochlear versus somatosensory) and may be related to ambiguous input to the CNS from injured sensory organs. Each can show improvement in the presence of a masking stimulus (acoustic for tinnitus, vibratory for pain). Both also show improvement with tricyclic treatment.

This improvement can be explained in at least two ways. Antidepressant treatment could reverse the demoralization that can accompany chronically aversive sensations. By reducing demoralization and increasing the ability of the host to cope with aversive stimuli, it could reduce the disability produced by these symptoms. Alternatively, antidepressant treatment could directly reduce the symptoms produced by a given injury. Two facts point to the notion that tricyclics have a direct analgesic action in patients with chronic pain that is independent of their antidepressant action. First, especially in the case of neuropathic pain, tricyclics often provide pain relief more quickly and at lower doses than depression relief.[28] Second, chronic pain of various types has been shown to respond to antidepressants in the absence of depression.[29]

The present study does not allow us to decide between these alternatives. Even audiometric tinnitus matching relies ultimately upon patient report of perceived sound levels and is therefore unable to distinguish between treatment effects upon the tinnitus sensation itself and the processes of symptom perception. It is possible that both were favorably affected in the present study. Further study with nondepressed but disabled tinnitus patients is necessary to sort out whether tricyclic treatment has effects upon tinnitus independent of its antidepressant effect.

We were surprised that the mean change in severity scores was so small (27%), since most patients felt the treatment was very beneficial, chose to continue nortriptyline for a recommended 6-month maintenance period (72%), and were uninterested in pursuing additional treatment modalities (58%). We suspect that our seven-point severity scale lacks sensitivity: frequently, subjects would select the same scale score on consecutive appointments while relating that the tinnitus was less bothersome. Some may have had difficulty distinguishing severity from loudness as well. In future trials, we will use new "externally referenced" severity and loudness scales designed to provide explicit definitions (behavioral and acoustic, respectively) for these variables.

Confusion between loudness and severity may have occurred with audiometric testing as well. The loudness of tinnitus matches decreased significantly with treatment. This could be an effect similar to the analgesic effect of tricyclics. It also could be that loudness may remain the same while subjects' criteria for comfortable and uncomfortable levels may change. Hinchcliffe and Chambers[30] found most comfortable loudness levels at 1,000 Hz (where patients' hearing was normal) to be lower in patients complaining of tinnitus than in normal subjects. We plan to pursue this by studying most comfortable loudness levels at 1,000 Hz before and after antidepressant therapy. We also will perform a tinnitus loudness match at 1,000 Hz in future subjects to try to overcome the fact that matches at different frequencies with different hearing thresholds make sensation level comparisons difficult to interpret.

Treatment recommendations based on the current study must be made with certain qualifications. We do not have follow-up data beyond 1 month for those patients who elected to continue taking nortriptyline. It is therefore not possible to provide documentation of continued compliance and effect. There are also no data on persistence of improvement following discontinuation of nortriptyline after 6 months (based upon treatment length recommended for major depression alone).

Nortriptyline was chosen for its favorable side effect profile and because it is possible to document therapeutic blood levels. Specifically, nortriptyline has not been shown to cause tinnitus, as have imipramine and protriptyline (hydrochloride). We expect that the other tricyclic antidepressants would show similar efficacy as they do in depression and chronic pain syndromes. Finally, tricyclic treatment appears to produce partial rather than total relief from tinnitus. The goal of such treatment should not be the eradication of tinnitus, but the restoration of the ability to accommodate to it as do most people with tinnitus.

REFERENCES

1. House JW. Management of the tinnitus patient. Ann Otol Rhinol Laryngol 1981;90:597-601.

2. House JW, Miller L, House PR. Severe tinnitus: treatment with biofeedback training (results in 41 cases). Trans Am Acad Ophthalmol Otolaryngol 1977;84:697-703.

3. Ireland CE, Wilson PH, Tonkin JP, Platt-Hepworth S. An evaluation of relaxation training in the treatment of tinnitus. Behav Res Ther 1985;23:423-30.

4. Hulshof JH, Vermeij P. The effect of intra-venous lidocaine and several different doses oral tocainide HCl on tinnitus. A dose-finding study. Acta Otolaryngol (Stockh) 1984;98:231-8.

5. Cathcart JM. Assessment of the value of tocainide hydrochloride in the treatment of tinnitus. J Laryngol Otol 1982;96:981-4.

6. Donaldson I. Tegretol: a double blind trial in tinnitus. J Laryngol Otol 1981;95:947-51.

7. Medical Research Council Institute of Hearing Research. Epidemiology of tinnitus. In: Evered D, Lawrenson GI, eds. Tinnitus: Ciba Foundation Symposium 85. London: Pitman Books, Ltd, 1981:16-34.

8. Coles RRA. Epidemiology of tinnitus: (1) prevalence. J Laryngol Otol [Suppl] 1984(suppl 9):7-15.

9. Axellson A, Ringdahl A. The occurrence and severity of tinnitus: a prevalence study. In: Feldmann H, ed. Proceedings III International Tinnitus Seminar. Karlsruhe, Federal Republic of Germany: Harsch Verlag, 1987:154-8.

10. Chung DY, Gannon RP, Mason K. Factors affecting the prevalence of tinnitus. Audiology 1984;23:441-52.

11. General household survey: the prevalence of tinnitus 1981. In: The Government Statistical Service OPCS Monitor. GSH 83/1, Feb 8, 1983.

12. Meikle MB, Vernon J, Johnson RM. The perceived severity of tinnitus: some observations concerning a large population of tinnitus clinic patients. Otolaryngol Head Neck Surg 1984;92:689-96.

13. Tyler RS, Baker LJ. Difficulties experienced by tinnitus sufferers. J Speech Hear Disord 1983;48:150-4.

14. Duckro PN, Pollard CA, Bray HD, Scheiter L. Comprehensive behavioral management of complex tinnitus: a case illustration. Biofeedback Self Regul 1984;9:459-69.

15. Stephens SD, Hallam RS. The Crown-Crisp Experiential Index in patients complaining of tinnitus. Br J Audiol 1985;19:151-8.

16. Lechtenberg R, Shulman A. The neurological implications of tinnitus. Arch Neurol 1984;41:718-21.

17. Reich GE, Johnson RM. Personality characteristics of tinnitus patients. J Laryngol Otol [Suppl] 1984(suppl 9):228-32.

18. Sullivan MD, Katon W, Dobie R, Sakai C, Russo J, Harrop-Griffiths J. Disabling tinnitus: association with affective disorder. Gen Hosp Psychiatry 1988;10:285-91.

19. Goodey RJ. Drugs in the treatment of tinnitus. In: Evered D, Lawrenson GI, eds. Tinnitus: Ciba Foundation Symposium 85. London: Pitman Books, Ltd, 1981:263-90.

20. Mihail RC, Crowley JM, Walden BE, Fishburne J, Reinwall JE, Zajtchuk JT. The tricyclic trimipramine in the treatment of subjective tinnitus. Ann Otol Rhinol Laryngol 1988;97:120-3.

21. Robins LN, Helzer JE, Crougham J, Ratcliff KS. National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. Arch Gen Psychiatry 1981;38:381-9.

22. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.

23. Derogatis LR. SCL-90 manual. Baltimore: Clinical Psychometric Research, 1977.

24. Kames LD, Naliboff BD, Henrich RL, Schag CC. The Chronic Illness Problem Inventory: problem-oriented psychosocial assessment of patients with chronic illness. Int J Psychiatry Med 1984;14:65-74.

25. Mathew RJ, Weinman ML, Mirabi M. Physical symptoms of depression. Br J Psychiatry 1981;139:293-6.

26. Wells KB, Burnam M, Golding J, et al. Profiles of health and functioning for depressed and non-depressed adult outpatients of mental health and medical clinicians. Presented at the meeting of the American Psychiatric Association, Chicago, May 10-14, 1987.

27. Romano J, Turner J. Chronic pain and depression: does the evidence support a relationship? Psychol Bull 1985;97:18-34.

28. Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith L, Warsh J. Amitriptyline versus placebo in postherpetic neuralgia. Neurology 1982;32:671-3.

29. Feinmann C. Pain relief by antidepressants: possible modes of action. Pain 1985;23:1-8.

30. Hinchcliffe R, Chambers C. Loudness of tinnitus: an approach to measurement. Adv Otorhinolaryngol 1983;29:163-73.

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MENIERE'S SYNDROME AND ENDOLYMPHATIC HYDROPS

DOUBLE-BLIND TEMPORAL BONE STUDY

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A systematic double-blind assessment of case histories and histopathologic findings in temporal bones in the collection at the Massachusetts Eye and Ear Infirmary was performed to test the hypothesis that clinical Meniere's syndrome is associated with endolymphatic hydrops demonstrated histopathologically at death. Thirteen of 13 cases of clinical Meniere's syndrome were found to have endolymphatic hydrops not attributable to other causes. However, some patients with idiopathic endolymphatic hydrops did not exhibit clinical Meniere's syndrome as revealed in their medical records. These results challenge the dogma that endolymphatic hydrops per se generates the symptoms of Meniere's syndrome.

KEY WORDS — endolymphatic hydrops, Meniere's disease, Meniere's syndrome, temporal bone histopathology.

INTRODUCTION

This is a report of a retrospective double-blind study correlating clinical case histories with histopathologic findings in temporal bones. The study was designed to test the hypothesis that clinical Meniere's syndrome is the direct consequence of idiopathic endolymphatic hydrops.

Prosper Meniere, in 1861, described a syndrome consisting of continuous or intermittent head noises accompanied by diminution of hearing and intermittent attacks of vertigo, dizziness, uncertain gait, staggering, and falling, accompanied by nausea, vomiting, and syncope.[1] The essence of Meniere's proposal was that the association of auditory and vestibular symptoms pointed to the ear as being the seat of the disorder, as opposed to the CNS. Meniere also observed that the external and middle ears appeared to be normal in such cases; so by extension from Flourens'[2] experiments on pigeons, he guessed the site of lesion to be the semicircular canals.

In 1938, Yamakawa[3] in Japan, and Hallpike and Cairns[4] in England, independently reported the finding of endolymphatic hydrops in temporal bones from patients with Meniere's syndrome. Hallpike and Cairns emphasized the apparent idiopathic nature of the hydrops that served to distinguish it from the hydrops due to labyrinthitis described earlier by Wittmaack.[5] Furthermore, hydrops was regarded as the "essential morbid anatomy of a specific disease of the labyrinth."[6] Subsequently, several investigators described similar temporal bone findings.[7-20] With the definition of a pathologic lesion, the term Meniere's "disease" came to be applied to the syndrome. In 1972, the Committee on Hearing and Equilibrium of the American Academy of Ophthalmology and Otolaryngology (AAOO)[21] incorporated this concept in its definition of Meniere's disease as being "a disease of the membranous inner ear characterized by deafness, vertigo, and usually tinnitus, and has as its pathologic correlate hydropic distension of the endolymphatic system." Thus, a central dogma has come to dominate current thinking: that although many possible etiologic factors can lead to endolymphatic hydrops, it is the hydrops that generates the symptoms of Meniere's syndrome (Fig 1[22]).

This central dogma, as Kiang[22] points out, has not been tested conclusively. "Strictly speaking, every clear-cut case of Menière's syndrome should have endolymphatic hydrops and every case of hydrops should show the clinical symptoms unless, of course, the chain of neural events is interrupted." There are reports of cases diagnosed as "Meniere's disease" during life that have shown no demonstrable endolymphatic hydrops at death.[23-27] Criteria to diagnose "Meniere's disease" vary widely, and one could argue that some of these did not represent true cases of "Meniere's disease." An alternate ex-

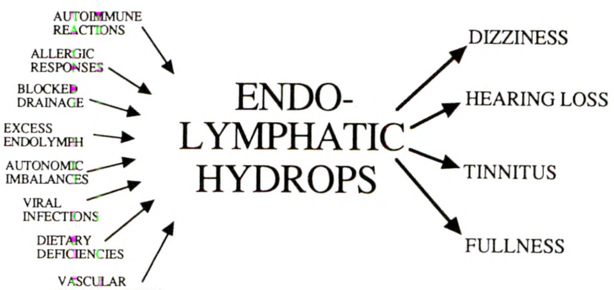

Fig 1. Central dogma for Meniere's syndrome. (Reprinted with permission.[22]) Many possible etiologic factors can lead to endolymphatic hydrops, which in turn generates clinical symptoms.

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planation is that whatever hydrops existed during life resolved in the time interval between diagnosis and death. It is recognized that endolymphatic hydrops is a well-documented pathologic entity[28] that can occur in association with several conditions, such as Mondini dysplasia, labyrinthitis, surgical trauma, and syphilis, and without any other recognizable predisposing histopathologic features. The latter group of idiopathic hydrops is supposedly responsible for symptoms of Meniere's syndrome. However, there have been instances in which idiopathic hydrops has been found in temporal bones of people who were not known to have exhibited the clinical symptoms of Meniere's syndrome.[27-29] Schuknecht and Gulya[28] believe that either such hydrops is nonprogressive or that spontaneous fistulization between endolymph and perilymph has occurred, thus explaining the absence of symptoms. Animal models for endolymphatic hydrops, such as in the guinea pig,[30,31] have shown that despite progressive hydrops, there are no observed episodic vestibular attacks, although continuous monitoring has not been reported.

The conflicting nature of some of these reports can be attributed, in part, to inherent inadequacies in studying human temporal bones. We believe that certain guidelines need to be fulfilled to allow meaningful interpretation of temporal bone data. 1) Accurate clinical documentation, close to time of death, is ideal. 2) Clinical and histologic criteria to define the entity being studied must be clearly laid out prior to data collection. 3) Correlation of clinical findings with histopathology should be free of preexisting bias; this is best achieved by double-blind assessments of data. 4) The number of cases studied should be adequate to allow for valid statistical analysis.

MATERIAL AND METHODS

The key to this study was the availability of a large collection of temporal bone sections at the Massachusetts Eye and Ear Infirmary along with the clinical medical records. Antemortem medical records including clinical histories, physical findings, and diagnostic test results of all cases for which the temporal bones were processed were reviewed. Cases were included in the study population if the medical record contained a thorough otologic history and both temporal bones were available. Each case selected for study was required to have adequate clinical documentation about the presence or absence of auditory and vestibular symptoms. (For instance, a case with documented sensorineural hearing loss but without mention of whether the patient had or did not have vertigo was rejected.) This preliminary screening yielded 125 cases (250 temporal bones).

Next, clinical scoring was done by one of the authors (B.A.T.) without knowledge of the histopathologic material. Eight categories of clinical features were analyzed in each case: demographics, hearing loss, vertigo, tinnitus, aural pressure, pertinent associated conditions, physical examination findings, and diagnostic test results. Demographic data included age, sex, race, time from death to fixation, age at otolaryngologic encounters, and whether or not the otolaryngologic examiner was trained at the Massachusetts Eye and Ear Infirmary. Descriptions of hearing loss included presence or absence of loss, laterality, progressive or stable loss, age at onset, rate of progression, fluctuation, and presence or absence of associated otologic symptoms for each ear. Data on vertigo included presence or absence; age at onset; duration; associated nausea or vomiting; descriptors of constant, episodic, positional, unsteadiness, or not specified; and presence or absence of associated otologic symptoms. Descriptions of tinnitus included presence, absence, or no comment; laterality; pitch; constant or intermittent; age at onset; and presence or absence of associated otologic symptoms for each ear. Descriptions of aural pressure included presence, absence or no comment; laterality, constant or intermittent; age at onset; and presence or absence of associated otologic symptoms for each ear. Pertinent associated conditions noted included otorrhea, meningitis, head trauma, ototoxic medications, congenital conditions, ear surgery, and other. Audiometric and vestibular test results, if available, were photocopied and appended to the clinical score sheets.

A four-part clinical summary was created for each case on the basis of the data collected from each medical record. This summary comprised a hearing loss description, a vertigo description, a tinnitus description, and pertinent clinical otologic diagnoses. Hearing loss summary description choices included none, conductive, sensorineural, mixed, fluctuating/sensorineural, and unspecified. Vertigo summary description choices included none, episodic, positional, constant, unsteadiness, episodic/positional, and unspecified. Tinnitus was summarized as present, absent, or no comment. Clinical otologic diagnoses included no evidence of disease, serous otitis media, chronic otitis media, otosclerosis, temporal bone fracture, acoustic trauma, labyrinthitis, presbycusis, ototoxicity, sudden hearing loss, mumps, measles, syphilis, multiple sclerosis, acoustic neuroma, Paget's disease, hereditary sensorineural hearing loss, vestibular neuronitis, Meniere's syndrome, benign paroxysmal positional vertigo, dysequilibrium of aging, cerebellopontine angle tumor, temporal bone tumor, metastatic brain tumor, sensorineural hearing loss (cause unknown), vertigo (probably peripheral), vertigo (probably central), vertigo (cause unknown), and tinnitus (cause unknown). The clinical diagnosis of Meniere's syndrome was made in strict accordance with AAOO guidelines.[21,32] Cases were required to involve both vertigo and hearing loss.

Vertigo was required to be a spontaneously occurring sensation of movement occurring in well-defined episodes. More than one episode was necessary. Each episode could be of varied severity, had to be frequently accompanied by nausea and sometimes vomiting, and had to be persistent for a prolonged period of time (20 minutes to no more than 24 hours). The patient had to be oriented and conscious throughout the episode and have no neurologic accompaniment or sequelae. The hearing loss was required to be sensorineural and progressive, and fluctuating in the early stages. Patients with only cochlear or vestibular symptoms, but not both, were not placed in the Meniere's syndrome group, but in separate categories.

All 125 cases meeting entry criteria for adequate antemortem clinical history and availability of both bones underwent histopathologic scoring. Complete temporal bone sets for each case were reviewed, and seven representative sections from each bone were selected by one of the authors (S.N.M.). These included midmodiolar for the cochlea, midmacular and mid-inferior utricular recess for the utricle, midmacular for the saccule, and midcristal for each of the three ampullae. All slide markings were masked and the slides presented in a coded order to one of the authors (S.D.R.), who scored the histopathologic findings according to a strict protocol. Thus, the slides for any one case would be mixed with all the slides of other cases in an order allotted by use of a random number table.

The position of the membranes of the endolymphatic labyrinth in each slide was scored as being normal, hydropic, ruptured, collapsed, or indeterminate. Hydrops was rated further as mild, moderate, or severe. Rupture was interpreted as normal, hydropic, or indeterminate. Collapse was interpreted as pathologic or artifactual. In the cochlea, the position of Reissner's membrane in each turn from base to apex was examined. Hydrops was defined as any convexity of the membrane (in direction of scala vestibuli). Each hydropic turn was scored as mild (convexity less than halfway to scalar wall of modiolus), moderate (convexity more than halfway to scalar wall of modiolus) or severe (membrane abutting scalar wall of modiolus). In the absence of volumetric reconstructions, objective criteria that define saccular, utricular, or ampullary hydrops are difficult to quantify. The ratings assigned in this study were based upon comparisons with normal temporal bone anatomy. Saccular hydrops was classified as being mild (dilatation of saccular membrane, but less than halfway to stapes footplate), moderate (dilatation more than halfway to stapes footplate), or severe (majority of saccular membrane abutting stapes footplate). Utricular and ampullary hydrops were judged to be mild (dilatation with minimal abutment of bony labyrinth wall) or severe (dilatation with majority of membrane abutting bony labyrinth wall). All of the histopathologic scoring was done without knowledge of any clinical information.

TABLE 1. TEST-RETEST RELIABILITY STATISTICS

	Expected Score	*Observed Score*	κ
Cochlea	0.28	0.92	0.89
Saccule	0.47	0.91	0.84
Utricle (midmacular)	*	1.00	1.00
Utricle (inferior recess)	0.68	0.80	0.38
Ampullae			
Superior	0.51	0.90	0.80
Lateral	0.73	0.95	0.82
Posterior	0.65	0.95	0.86

*When there was no test-retest variance, expected score was not calculated.

Endolymphatic hydrops in a temporal bone was defined, for the purpose of this study, as hydrops present in any part of the membranous labyrinth with the exception of pure apical cochlear hydrops. This was based on the observations by Yamashita and Schuknecht[33] that pure apical endolymphatic hydrops occurs in about 15% of human cochleae; that it cannot be correlated with any type of ear disease; and that it is probably of no pathologic or functional significance. After completion of histopathologic scoring, complete sets of slides of bones with endolymphatic hydrops were reviewed (by scorers still blinded to the clinical histories) to determine whether the hydrops appeared to be "idiopathic" (without recognizable predisposing pathologic features) or "secondary" to factors (such as surgical trauma, labyrinthitis, and syphilis) known to be associated with hydrops.

Internal consistency of histopathologic scoring was tested by presentation of 8% of the sections for randomly repeated scoring without informing the scorer that sections could be repeated. Sections repeated were divided equally among cochleae, sacculi, utriculi, and ampullae. About 80% had been scored as "normal" and 20% "pathologic" at the time of the first scoring. Test-retest reliability was determined by use of the kappa (κ) statistic according to generally accepted standards as described by Landis and Koch.[34]

Thus, the clinical scoring, random coding of slides, and histopathologic scoring were each performed by three different individuals (B.A.T., S.N.M., and S.D.R., respectively) with rigid adherence to the double-blind protocol to prevent scoring bias. After all of the scoring for clinical reports and temporal bone sections was completed, the code was broken and the data were analyzed.

RESULTS

First, data from the histopathology phase of the work will be presented. Test-retest reliability (κ) statistics are detailed in Table 1. Kappa values of

TABLE 2. DISTRIBUTION OF ENDOLYMPHATIC HYDROPS VERSUS CLINICAL DIAGNOSIS OF MENIERE'S SYNDROME

	Hydrops Present	*Hydrops Absent*
Meniere's syndrome	13	0
No Meniere's syndrome	6	100

Cases of secondary hydrops omitted (see text).

>0.75 are considered excellent agreement between test and retest. Values of 0.40 to 0.75 are fair to good and values <0.40 are low agreement. Values of κ ranged from 0.80 to 1.0 for cochlear, saccular, mid-macular utricular, and all midampullary scores. Mid-inferior utricular recess scores had a κ value of 0.38. Thus, with the single exception of the inferior utricular recess, there is excellent test-retest reliability for the histopathologic scoring system.

Twenty-five patients were scored as having endolymphatic hydrops in at least one ear. Six of these were scored as having secondary hydrops on the basis of coexistence of other pathologic changes in their temporal bones. Two patients (cases 13 and 85) had surgical trauma to the inner ear from stapedectomy, one (case 40) had labyrinthitis due to active erosive chronic otitis media with osteitis, one (case 90) had tertiary syphilis, one (case 46) had intralabyrinthine acoustic neuroma, and one (case 83) had multiple histopathologic abnormalities including endolymphatic hydrops, cupulolithiasis of the posterior ampulla, acoustic neuroma, and arachnoid cyst with degeneration of vestibular nerves that precluded accurate comparisons between symptoms and histopathology. The 19 remaining patients had idiopathic endolymphatic hydrops in at least one ear. Of these, 13 had clinical Meniere's syndrome (Table 2). The ratio of male to female in this subset was 7:6, with an average age of 70 years (range, 58 to 83). Six patients with idiopathic endolymphatic hydrops in at least one ear did not carry a clinical diagnosis of Meniere's syndrome. All were male and the average age was 66 years (range, 35 to 91).

There were seven cases of episodic vertigo without associated hearing loss or neurologic manifestations. Of these, three (cases 26, 114, and 119) involved episodic vertigo of a nature indistinguishable from that of clinical Meniere's syndrome: spinning vertigo with nausea and vomiting lasting minutes to hours (so-called "vestibular" Meniere's[21]). None of these three patients had endolymphatic hydrops; two had no observable histopathologic changes in their temporal bones, and one had atrophy of the lateral ampullary nerve. Each of the four remaining patients (cases 6, 45, 78, and 106) had episodic vertigo lasting less than 5 minutes. Again, none had endolymphatic hydrops; two had cupulolithiasis of the posterior ampulla, one had pathologic collapse of the vestibular membranous labyrinth, and one had no observable histopathologic abnormalities. In our study population there were no cases of documented fluctuating sensorineural hearing loss without vertigo (so-called "cochlear" Meniere's[21]).

Each and every patient assigned a clinical diagnosis of Meniere's syndrome had idiopathic cochleosaccular hydrops in at least one ear (Table 3). Five of these 13 cases had bilateral cochleosaccular hydrops. Eight of the 13 also had additional utricular and/or ampullary hydrops in the afflicted ear. In all patients with unilateral endolymphatic hydrops the hydropic ear had worse hearing; all patients with bilateral endolymphatic hydrops had bilateral hearing loss. Of a total of 127 cochlear turns rated in the Meniere's temporal bones, 78 (61.4%) were hydropic, of which three (3.8%) were rated as mild, 23 (29.5%) moderate, and 47 (60.3%) severe, and five (6.4%) showed rupture with hydrops. Seventeen of 26 (65.4%) sacculi were hydropic, of which one (5.9%) was mild, two (11.8%) were moderate,

TABLE 3. HISTOPATHOLOGIC SCORES IN 13 CASES ASSIGNED CLINICAL DIAGNOSIS OF MENIERE'S SYNDROME

	Right Ear											*Left Ear*										
	Cochlear Turns						*Utricle*		*Ampullae*			*Cochlear Turns*						*Utricle*		*Ampullae*		
	1	*2*	*3*	*4*	*5*							*1*	*2*	*3*	*4*	*5*						
Case	*Base*		*Middle*		*Apex*	*Saccule*	*A*	*B*	*S*	*L*	*P*	*Base*		*Middle*		*Apex*	*Saccule*	*A*	*B*	*S*	*L*	*P*
17	4	4	4	3	4	4	1	10	8	1	6	4	4	4	4		4	1	1	2	2	6
23	1	1	9	1	10	1	1	1	1	1	1	4	9	9	9	2	2	1	10	1	1	1
25	4	3	6	4		4	9	9	1	1	1	1	4	1	3		4	1	1	1	1	1
27	4	4	4	4	4	10	2	10	6	1	6	4	4	4	4	6	4	2	4	2	6	6
32	1	1	1	1	3	7	1	5	1	1	9	4	4	4	4	4	4	7	2	1	7	1
55	10	10	10	10	10	7	10	7	10	1	7	9	4	6	4	4	6	10	2	10	10	1
56	1	1	1	1	1	1	1	5	1	1	1	6	4	6	10	10	4	1	5	1	5	1
61	3	3	3	2	9	3	1	1	1	1	1	1	1	1	1	1	5	1	1	9	1	1
70	7	9	9	1	2	1	1	1	1	1	1	3	3	3	3	4	6	1	6	1	1	1
72	1	1	1	1	1	1	1	1	1	1	1	4	4	4	4	4	4	2	1	6	6	2
87	4	3	9	3	3	3	1	1	9	1	9	3	3	1	3	3	4	9	10	9	9	9
108	1	1	1	1	1	5	9	5	1	1	1	4	4	4	4	4	4	4	4	8	6	4
124	4	4	4	4	4	4	6	6	6	6	6	3	3	3	3	3	4	2	6	1	6	1

A — midmacular, B — mid-inferior utricular recess, S — superior, L — lateral, P — posterior, 1 — normal, 2 —mild hydrops, 3 — moderate hydrops, 4 — severe hydrops, 5 — rupture (normal), 6 — rupture (hydrops), 7 — rupture (indeterminate), 8 — pathologic collapse, 9 — artifactual collapse, 10 — could not be scored.

TABLE 4. HISTOPATHOLOGIC SCORES IN SIX CASES OF IDIOPATHIC HYDROPS IN AT LEAST ONE EAR NOT ASSIGNED CLINICAL DIAGNOSIS OF MENIERE'S SYNDROME

	Right Ear											*Left Ear*										
	Cochlear Turns											*Cochlear Turns*										
	1	*2*	*3*	*4*	*5*		*Utricle*		*Ampullae*			*1*	*2*	*3*	*4*	*5*		*Utricle*		*Ampullae*		
Case	*Base*		*Middle*		*Apex*	*Saccule*	*A*	*B*	*S*	*L*	*P*	*Base*		*Middle*		*Apex*	*Saccule*	*A*	*B*	*S*	*L*	*P*
9	1	1	9	9	9	9	1	1	1	1	1	3	6	6	3	4	4	1	5	2	6	1
36	9	9	9	1	9	9	1	1	1	1	1	9	9	9	9	9	2	1	1	1	1	1
39	1	1	1	1	1	2	1	1	1	1	1	1	1	9	1	1	9	1	1	1	1	1
62	1	2	1	1	3	6	2	1	2	1	2	3	3	3	2	3	4	2	8	8	8	8
93	9	9	9	9	1	9	1	1	1	1	1	9	9	9	2	3	1	1	1	1	1	1
94	4	4	4	4	4	4	4	1	2	6	4	4	4	4	4	4	4	6	1	1	1	1

A — midmacular, B — mid-inferior utricular recess, S — superior, L — lateral, P — posterior, 1 — normal, 2 — mild hydrops, 3 — moderate hydrops, 4 — severe hydrops, 5 — rupture (normal), 6 — rupture (hydrops), 8 — pathologic collapse, 9 — artifactual collapse.

and 12 (70.5%) were severe, and two (11.8%) showed rupture with hydrops. Thirty-one of 130 (23.8%) utriculoampullary sections were hydropic, with ten (32.3%) mild, and four (12.9%) severe, and 17 (54.8%) scored as having rupture with hydrops.

Two of the six non-Meniere idiopathic endolymphatic hydrops group (Table 4) showed only mild unilateral saccular hydrops (cases 36 and 39). One patient had mild unilateral cochlear hydrops (case 93). The other three cases (9, 62, and 94) in this group showed diffuse endolymphatic hydrops with preservation of neurosensory elements in at least one ear. The hydropic changes in their membranous labyrinths were similar in location and severity to those in temporal bones from patients with Meniere's syndrome (Fig 2). Of a total of 20 cochlear turns (from ears with histopathologic evidence of viable neurosensory elements) in these latter three cases, 12 (60.0%) were hydropic, of which one (8.3%) was rated as mild, three (25.0%) moderate, and six (50.0%) severe, and two (16.7%) showed rupture with hydrops. Three of four (75.0%) sacculi in this group were hydropic, with one (33.3%) showing rupture with hydrops and the other two (66.7%) being severely hydropic. Nine of 20 (45.0%) utriculoampullary sections were hydropic, with five (55.6%) mild and two (22.2%) severe, and two (22.2%) scored as having rupture with hydrops. The six non-Meniere hydropic cases will now be described in more detail.

CASE DESCRIPTIONS

CASE 9

At the age of 78 this man was hospitalized for treatment of squamous cell carcinoma of his right maxillary sinus. He reported having hearing loss in both ears for several years, and that it was worse on the left. He had occasional tinnitus. He denied vertigo. He had a history of exposure to noise as a factory worker. An audiogram 6 days before death showed a gently down-sloping, moderate to severe sensorineural hearing loss in the right ear and a severe to profound sensorineural hearing loss, worse in the low frequencies, in the left ear. Speech discrimination was 92% on the right and 60% on the left. He died of cardiopulmonary arrest.

Histopathology of Right Inner Ear. Reissner's membrane is collapsed onto the organ of Corti in the middle and apical turns. The hair cell population and stria vascularis appear to be normal. There is partial loss of cochlear neurons in the basal turn. The saccular wall is partially collapsed (artifactual) onto the macula. The saccular macula appears normal. The utricle and ampullae, their neurosensory elements, the vestibular nerves, and the bony labyrinth appear normal.

Histopathology of Left Inner Ear. There is moderate to severe endolymphatic hydrops in all cochlear turns. There are tears of the basilar membrane. The hair cell population of the organ of Corti and the stria vascularis appear normal. There is a partial loss of cochlear neurons in the basal turn. There is severe hydrops of the saccule; its wall has herniated into the common crus and appears to compress the utriculoendolymphatic valve. The saccular macula appears normal. The utricle and its macula appear normal. There is mild hydrops of the superior ampulla and hydrops with rupture of the lateral ampulla. The posterior ampulla appears normal. All cristae, vestibular nerves, and the bony labyrinth appear normal.

COMMENT. This patient had bilateral severe sensorineural hearing loss without vertigo. He received a diagnosis of presbycusis in our clinical summary. There are no observable histopathologic changes in the inner ears to explain his hearing loss. There is moderately severe endolymphatic hydrops in the left ear involving the cochlea, saccule, and ampullae with preservation of neurosensory elements.

CASE 36

At the age of 74 this man complained of gradually progressive hearing loss in both ears for 4 years with tinnitus (side not specified). He denied vertigo. The left tympanic membrane was thickened and the right showed a dry subtotal perforation. Audiometry showed a bilateral, symmetric, flat, severe sensorineural hearing loss with a superimposed con-

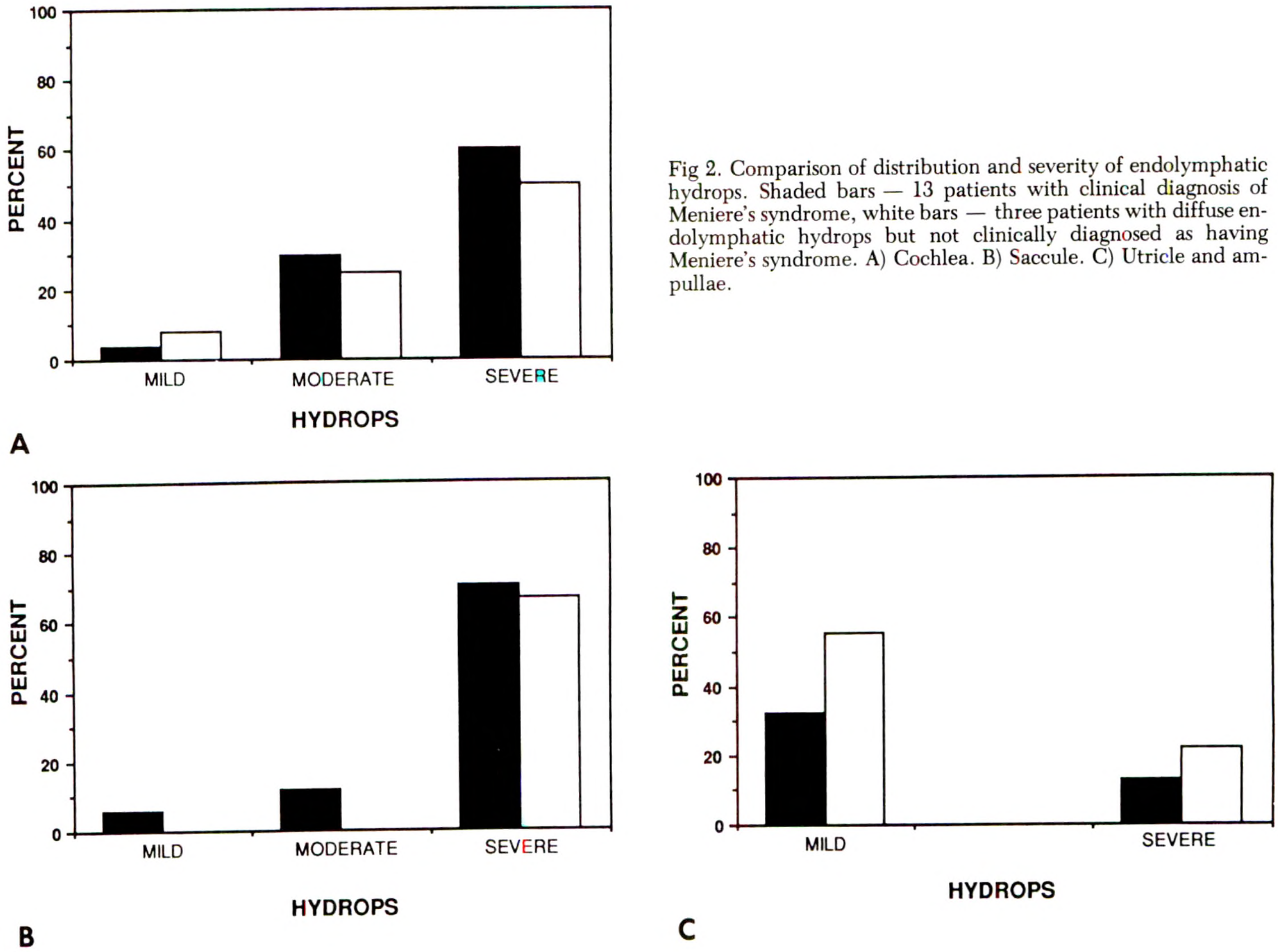

Fig 2. Comparison of distribution and severity of endolymphatic hydrops. Shaded bars — 13 patients with clinical diagnosis of Meniere's syndrome, white bars — three patients with diffuse endolymphatic hydrops but not clinically diagnosed as having Meniere's syndrome. A) Cochlea. B) Saccule. C) Utricle and ampullae.

ductive component on the right. Speech discrimination scores were 54% on the right and 40% on the left. He died 5 years later of pulmonary edema.

Histopathology of Right Inner Ear. Reissner's membrane is collapsed onto the organ of Corti in most turns. There is scattered loss of outer hair cells in the basal turn. The stria vascularis shows large areas of patchy atrophy in the apical half of the cochlea. There is a loss of about 20% of cochlear neurons in the basal turn and about 30% to 40% in the middle and apical turns. The saccular wall is partially collapsed (artifactual). The saccular macula appears normal. The utricular and ampullary membranes and their sense organs, the vestibular nerves, and the bony labyrinth appear normal.

Histopathology of Left Inner Ear. Reissner's membrane is collapsed onto the organ of Corti in all turns. There is scattered loss of outer hair cells in the basal turn. The stria vascularis is atrophic in the apical half of the cochlea. There is a loss of about 20% of cochlear neurons in the basal turn and about 30% to 40% in the middle and apical turns. There is mild hydrops of the saccule with proliferation of cellular tissue that bridges across its lumen from the otoconia to the lateral membranous wall. It consists of clumps and sheets of cells with amorphous, lightly staining, basophilic material scattered in between. The nature of this tissue is unclear. The saccular macula appears normal. The utricle and its macula, all ampullae and their cristae, the vestibular nerves, and the bony labyrinth appear normal.

COMMENT. This patient had bilateral severe sensorineural hearing loss without vertigo. He was assigned clinical diagnoses of presbycusis and chronic otitis media. The sensorineural hearing loss can be explained on the basis of strial atrophy and loss of cochlear neurons. There is mild saccular hydrops on the left with preservation of neurosensory elements.

CASE 39

At the age of 46 this man experienced the simultaneous onset of sudden vertigo, tinnitus, and hearing loss in both ears. The vertigo resolved within 24 hours. Hearing returned to normal in the left ear within 12 hours, but the loss persisted in the right ear. Findings of the otologic examination were otherwise negative. An audiogram taken 5 days later showed a severe, flat, sensorineural hearing loss in the right ear with 0% speech discrimination. He was hospitalized and treated with intravenous histamine and Rheomacrodex. Serial audiograms showed hearing improvement over a 5-day period to a mild, low frequency, sensorineural hearing loss with 60% discrimination. By the following day, hearing was subjectively normal. He died 2 days later of acute renal failure.

Histopathology of Right Inner Ear. Reissner's membrane appears in its normal position. The hair cell population of the organ of Corti, stria vascularis, and cochlear neuronal population appear normal. There is mild hydrops of the saccule, with a wide opening into the endolymphatic sinus. The saccular macula appears normal. The utricle and ampullae and their sense organs, the vestibular nerves, and the bony labyrinth appear normal.

Histopathology of Left Inner Ear. There is collapse of Reissner's membrane onto the organ of Corti in the middle turn. The hair cell population of the organ of Corti, the stria vascularis, and the cochlear neuronal population appear normal. The saccule opens widely into the endolymphatic sinus. Its wall appears to be artifactually collapsed onto the macula. The saccular macula appears normal. The utricle and ampullae and their sense organs, the vestibular nerves, and the bony labyrinth appear normal.

COMMENT. This patient was assigned diagnoses of sudden hearing loss and vertigo (cause unknown) in our clinical summary. Both inner ears appear to be normal except for mild saccular hydrops on the right side. There is no clear histopathologic indication as to what caused the vertigo and bilateral hearing loss. The simultaneous and sudden onset of hearing loss in both ears and gradual recovery of hearing in one ear over a 10-day interval are inconsistent with a clinical diagnosis of Meniere's syndrome.

CASE 62

At the age of 31 this man stated that he had had a profound hearing loss in his left ear since childhood that he attributed to mumps. He complained of constant, low-pitched tinnitus in his right ear and fluctuating hearing on that side related to episodes of nasal congestion. The findings on otologic examination were normal. Audiometry showed a profound left-sided sensorineural hearing loss and normal hearing on the right with 100% speech discrimination. At the age of 34 he complained of tinnitus in his right ear for 5 days following an upper respiratory tract infection. He denied hearing loss in the right ear and denied vertigo. An audiogram again revealed the unilateral left profound hearing loss. There was also a mild, low frequency sensorineural hearing loss in the right ear (decrease of 15 dB at 250 Hz and 5 dB at 500 Hz compared to the audiogram done 4 years earlier). Speech discrimination was 100% on the right. He died 5 months later of bronchopulmonary aspiration and cardiac arrest.

Histopathology of Right Inner Ear. There is mild endolymphatic hydrops in the upper basal turn of the cochlea and moderate hydrops in the apical turn. The hair cell population of the organ of Corti, the stria vascularis, and the cochlear neuronal population appear normal. There is hydrops with rupture of the saccule. Most of the saccular macula appears normal. There is a small, localized area of atrophy in the anterior third of the macula with cellular encapsulation of the overlying otolithic membrane. There is mild hydrops of the utricle, superior ampulla, and posterior ampulla. The macula of the utricle and all cristae appear normal. The vestibular nerve fibers and bony labyrinth appear normal.

Histopathology of Left Inner Ear. There is moderately severe endolymphatic hydrops involving all turns of the cochlea. There are only scattered hair cells present in the middle and apical turns. The tectorial membrane is spherically deformed and encapsulated in the basal and middle turns and is missing in parts of the middle and apical turns. There is partial patchy atrophy of the stria vascularis. There is partial loss of cochlear neurons in the basal turn. The saccule shows severe endolymphatic hydrops, with complete degeneration of its macula. The utricle is also hydropic, with severe atrophy of its macula. The ampullary walls are distorted as a result of pathologic collapse. All cristae are severely atrophic. There is a loss of about 50% of the vestibular neurons. The bony labyrinth appears normal.

COMMENT. The diagnoses assigned in our clinical summary were sensorineural hearing loss in the left ear due to mumps and eustachian tube dysfunction on the right. It is possible that there was an insult to the inner ear during childhood that destroyed all auditory and vestibular function in the left ear. Hence, the endolymphatic hydrops in that ear would be asymptomatic. On the contralateral side, there is hydrops of the cochlea, saccule, utricle, and ampullae with apparent preservation of neurosensory elements.

CASE 93

This man was examined at the age of 65 for recurrent dizzy spells for 5 years. He felt off balance, as if he might fall. The spells lasted for 1 to 1½ minutes, after which he felt unsteady for another 5 minutes. Sitting up rapidly provoked transient dizziness, sometimes with nausea. He also had neurologic symptoms including bitemporal and vertex headaches, paresthesias and pain in the left upper extremity, incoordination of the left hand, and dysphagia. Results of otologic and neurologic examinations were normal except for positional testing, which provoked brief vertigo and nausea on sitting up but without nystagmus. There was a loud, harsh, systolic bruit in the left supraclavicular area. Audiometry showed bilateral sensorineural hearing loss. On the right, there was a flat 20-dB loss to 1,000 Hz and a flat loss of 50 to 60 dB from 2,000 to

8,000 Hz. On the left, there was an ascending-pattern hearing loss for frequencies below 1,000 Hz and a descending pattern for frequencies above 1,000 Hz. Speech discrimination scores were 88% on the right and 90% on the left. Bithermal caloric testing showed a borderline reduced vestibular response (20% difference) on the left. Angiography revealed an ulcerated atherosclerotic plaque at the origin of the left subclavian artery with slight stenosis of the origin of the left vertebral artery. These changes were judged hemodynamically insignificant. Fifteen months later the patient complained of increasing dizziness and headaches. He also complained of progression of hearing loss that was worse on the left. He had occasional visual disturbance in the left visual field with brief horizontal diplopia. Neurologic examination showed incoordination of the left hand with unsteadiness on tandem walking. The Rinne test was positive bilaterally and the Weber lateralized to the left. He died 1 month later of cerebral infarction.

Histopathology of Right Inner Ear. Reissner's membrane is collapsed onto the organ of Corti in all turns except the apical. The hair cell population of the organ of Corti appears normal except for mild scattered loss in the upper basal turn. There is patchy atrophy of the stria vascularis in the apical half of the cochlea. The cochlear neuronal population appears normal. There is partial collapse (artifactual) of the saccular wall. The saccular macula, the utricle and its macula, all ampullae and their cristae, the vestibular nerve fibers, and the bony labyrinth appear normal.

Histopathology of Left Inner Ear. There is mild endolymphatic hydrops of the upper middle turn of the cochlea and moderate hydrops of the apical turn. In the lower middle and basal turns, Reissner's membrane is partially collapsed onto the organ of Corti. The hair cell and cochlear neuronal populations appear normal. There is partial patchy atrophy of the stria vascularis in the apical half of the cochlea. The saccular wall is folded back on itself, and it is possible that it was mildly hydropic during life. The saccular macula appears normal. The vestibular nerve trunks have been avulsed from the internal auditory canal. The vestibular nerve fibers as judged by their appearance in the cribrose areas appear normal. The bony labyrinth appears normal.

COMMENT. This patient was assigned a clinical diagnosis of vertigo (cause unknown). There is mild hydrops of the cochlea and possibly of the saccule in the left ear, with normal-appearing neurosensory structures. The clinical symptoms do not meet the AAOO criteria for Meniere's syndrome. It is possible that the vertigo was central in origin.

CASE 94

At the age of 78 this man presented for evaluation of a right-sided hearing loss of 7 weeks' duration that had evolved over a 1-week period. He reported having hearing loss in the left ear since the age of 20. Results of an otologic examination were normal. Audiometry showed a bilateral, flat, symmetric, 70-dB sensorineural hearing loss with speech discrimination scores of 4% on the right and 28% on the left. At age 84, repeat audiometry showed a symmetric 10-dB progression of the hearing loss in both ears, with speech discrimination scores of 20% in each ear. At this time he denied vertigo and tinnitus. He died at age 91 of renal failure.

Histopathology of Right Inner Ear. There is severe endolymphatic hydrops throughout the cochlea. The organ of Corti has hair cells throughout all turns. There is severe atrophy of the stria vascularis in all turns. There is a partial loss of cochlear neurons in the basal turn. There is severe hydrops of the saccule, and its wall has herniated deeply into the common crus. There is proliferation of fibrous tissue on the vestibular side of the stapes footplate. The utricle is severely hydropic. The saccular and utricular maculae appear normal. There is hydrops of all ampullae. The cristae appear normal. The vestibular nerve trunks have been avulsed from the internal auditory canal; however, the vestibular nerve fibers appear to be normal in all cribrose areas. The bony labyrinth is normal.

Histopathology of Left Inner Ear. There is severe endolymphatic hydrops throughout the cochlea. There are hair cells present throughout the organ of Corti. The stria vascularis is severely atrophic in all turns. There is partial loss of cochlear neurons in the basal turn. There is severe hydrops of the saccule with a thick layer of irregularly granular, basophilic material between its wall and the macula. There are areas of focal degeneration of the saccular macula. There is hydrops with rupture of the utricle. There is partial loss of sensory cells of the utricular macula. The ampullary walls appear to be normal. There is severe loss of sensory cells in all cristae; only supporting cells remain. There is severe degeneration of the vestibular nerve fibers as judged by their appearance in the cribrose areas. The bony labyrinth appears normal.

COMMENT. This patient was assigned a clinical diagnosis of presbycusis. He had no vertigo, despite having bilateral, severe, diffuse, endolymphatic hydrops with preservation of neurosensory elements on the right side.

DISCUSSION

The objective of this study was to utilize strict adherence to a double-blind research protocol to assess whether a correlation exists between the clinical diagnosis of Meniere's syndrome and the histopathologic finding of endolymphatic hydrops. The finding that endolymphatic hydrops (at least cochleosaccular) was present in 100% of temporal bones from patients with the clinical diagnosis of Meniere's syndrome establishes this correlation. Such a correlation, however, does not imply a cause-and-effect relationship. The central dogma of endolymphatic hydrops as the common pathway between cause and clinical symptoms implies that all patients with clinical Meniere's syndrome should have endolymphatic hydrops and that all patients with endolymphatic hydrops should manifest the syndrome, unless some other factor blocks or masks development of the typical symptoms of fluctuating, progressive sensorineural hearing loss, episodic vertigo, and tinnitus. Our finding of cases meeting the histopathologic criteria for endolymphatic hydrops but failing to demonstrate the clinical presentation of Meniere's syndrome raises questions about the validity of this dogma. If the dogma is to survive, some explanation must be offered to account for the absence of clinical Meniere's syndrome in such cases.

It is possible that loss of peripheral neurosensory elements (perhaps at the submicroscopic level) or some CNS disorder affecting the auditory and/or vestibular pathways might mask or block the appearance of clinical symptoms. Also, there are vulnerabilities inherent in any retrospective study, such as the presence of clinical symptoms not observed or documented in the medical record. Alternatively, symptoms may have developed during the interval between the last otologic examination and death. Our study protocol was designed to minimize such possibilities. The patients in cases 9, 62, and 94 had their last otologic encounters 6 days, 5 months, and 5½ years prior to death, at which time they denied suffering from vertigo. Another possible explanation is inadequate time between development of hydrops and death to permit onset of clinical symptoms. Schuknecht and Gulya[28] proposed that asymptomatic endolymphatic hydrops could be explained by hydrops that did not progress to rupture or by the development of spontaneous permanent fistulization of the membranous labyrinth. An integral part of this explanation is the concept that progressive endolymphatic distension results in ruptures of the membranous labyrinth that in turn cause symptoms by contamination of the perilymphatic space with endolymph. The concept of membrane rupture as the essential pathophysiologic mechanism remains a viable hypothesis as far as our results are concerned, although it may present other difficulties.[35,36] It would be necessary to survey complete sets of serial sections of the entire membranous labyrinth to assess the incidence and location of ruptures accurately. Furthermore, it is difficult to determine with certainty whether such ruptures are pathologic or artifactual. Finally, the possibility of healed ruptures is difficult to assess. In any case, the concept that cochleosaccular hydrops is a precondition for rupture that leads to the expression of both auditory and vestibular symptoms remains intact.

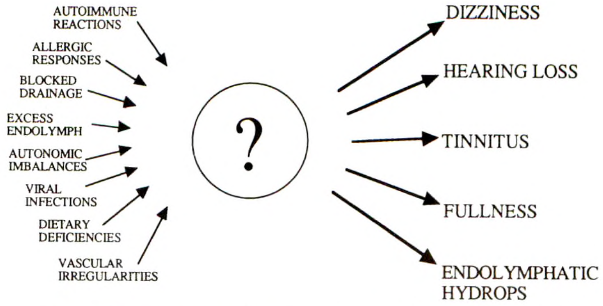

Fig 3. Proposed modification of central dogma for Meniere's syndrome: some factor or number of factors (as yet unknown) that affect fluid management within inner ear produces both clinical symptoms and endolymphatic hydrops.

It is conceivable that some factor or number of factors that affect fluid management within the inner ear produce both the clinical symptoms of Meniere's syndrome and endolymphatic hydrops, in which case the hydrops would be an epiphenomenon (Fig 3). Prime candidates include metabolic, biochemical, and hydrostatic alterations. Such possible factors, however, remain vague and speculative at the present time. Until the pathophysiology is better understood, we must admit that we cannot account for the association of episodic vertigo and hearing loss with endolymphatic hydrops.

Current therapeutic techniques for Meniere's syndrome can be divided broadly into destructive procedures and methods aimed at amelioration of hydrops. Destructive procedures such as labyrinthectomy and vestibular neurectomy clearly have a higher success rate than approaches meant to control hydrops, such as diuretics or salt restriction, sac drainage or decompression, and round window cochleosacculotomy. If indeed the development of endolymphatic hydrops is an epiphenomenon of the development of hearing loss and vertigo, then there is no clear rational basis for therapy to relieve hydrops per se. The reported success rates of hydrops-relieving therapies are all in the range of 60% to 80%,[37] which is close to the reported rate of spontaneous remission (71%) of Meniere's symptoms.[38]

This study is obviously only an initial step. The number of cases available for analysis was small, despite our having reviewed the entire temporal bone collection at the Massachusetts Eye and Ear Infirmary. More powerful conclusions may be drawn by continuation of this study by application of the same protocol to other temporal bone collections. The more difficult questions of possible correlation of histopathology with specific symptoms or with the course of disease, evaluation of the role of membrane ruptures, interpretation of diagnostic test results, and examination of the scientific basis of therapy will require well-controlled prospective clinical studies with detailed data acquisition and careful postmortem temporal bone analysis. In particular, the practicing physician might do well to inquire specifically about the occurrence of tinnitus or "fullness" in the ear, and record a detailed description of these symptoms when present. We had to omit these symptoms from our study because of the infrequency of notation as to whether the questions were asked by the physicians.

CONCLUSION

This study shows that clinical Meniere's syndrome and cochleosaccular endolymphatic hydrops demonstrated histopathologically at death are closely related. The full-blown, classic case of Meniere's syndrome with both auditory and vestibular symptoms apparently has an inevitable pathologic correlate in idiopathic endolymphatic hydrops. However, idiopathic endolymphatic hydrops need not be accompanied by an expression of the symptoms of Meniere's syndrome. It seems prudent to reevaluate the connection between endolymphatic hydrops and the clinical symptoms of Meniere's syndrome.

One direct way to confirm or refute these observations will lie in the future ability to image the endolymphatic space in living subjects. Kiang[22] points out that the differences in chemical composition among endolymph, perilymph, and soft tissues might make it possible someday to image the endolymphatic space with sufficient resolution to monitor its shape in people with Meniere's syndrome so that the dynamic events could be followed over time. Such technical advances would relieve us of the present constraint of trying to correlate medical histories involving many years with the histopathologic appearance of temporal bone structures at one point in time.

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REFERENCES

1. Atkinson M. Meniere's original papers. Reprinted with an English translation together with commentaries and biographical sketch. Acta Otolaryngol [Suppl] (Stockh) 1961(suppl 162).

2. Flourens MJP. Expériences sur les canaux semi-circulaires de l'oreille. Mem Acad Sci 1830;9:455-77.

3. Yamakawa K. Über die pathologische Veränderung bei einem Meniere-Kranken. J Otorhinolaryngol Soc (Jpn) 1938;44:2310-2.

4. Hallpike CS, Cairns H. Observations on the pathology of Menière's syndrome. J Laryngol Otol 1938;53:625-55.

5. Wittmaack K. Hydrops labyrinthi (Labyrinthitis serosa). In: Henke F, Lubarsch O, eds. Handbuch der speziellen pathologischen Anatomie und Histologie. Berlin: Verlag von Julius Springer, 1926:290-307.

6. Hallpike CS, Wright AJ. On the histological changes in the temporal bones of a case of Ménière's disease. J Laryngol Otol 1940;55:59-66.

7. Rollin H. Zur Kenntnis des Labyrinthhydrops und des durch ihn bedingten Ménière. Der Hals-Nasen-und Ohrenarzt 1940;31:73-109.

8. Lindsay JR. Labyrinthine dropsy and Ménière's disease. Arch Otolaryngol 1942;35:853-67.

9. Altmann F, Fowler EP Jr. Histological findings in Ménière's symptom complex. Ann Otol Rhinol Laryngol 1943;52:52-80.

10. Lindsay JR. Ménière's disease. Histopathologic observations. Arch Otolaryngol 1944;39:313-8.

11. Lindsay JR. Labyrinthine dropsy. Laryngoscope 1946;56:325-41.

12. Cawthorne T. Ménière's disease. Ann Otol Rhinol Laryngol 1947;56:18-38.

13. Day KM, Lindsay JR. Hydrops of the labyrinth. Case report. Coagulation operation, clinical course and histopathology. Laryngoscope 1949;59:213-27.

14. Nager FR. Zur Histopathologie des Ohrschwindels. Pract Oto-Rhino-Laryngol 1949;11:360-77.

15. Hallpike CS, Harrison MS. Ménière's disease treated by Portmann's operation. Report and clinicopathological study of a case. Arch Otolaryngol 1954;60:141-4.

16. Lindsay JR, Schulthess GV. An unusual case of labyrinthine hydrops. Acta Otolaryngol (Stockh) 1958;49:315-24.

17. Lawrence M, McCabe BF. Inner ear mechanics and deafness. Special consideration of Meniere's syndrome. J Am Med Assoc 1959;171:1927-32.

18. Kristensen HK. Histopathology in Ménière's disease. Acta Otolaryngol (Stockh) 1961;53:237-48.

19. Schuknecht HF, Benitez JT, Beekhuis J. Further observations on the pathology of Menière's disease. Ann Otol Rhinol Laryngol 1962;71:1039-53.

20. Altmann F, Kornfeld M. Histological studies of Menière's disease. Ann Otol Rhinol Laryngol 1965;74:915-43.

21. Alford BR. Meniere's disease: criteria for diagnosis and evaluation of therapy for reporting. Trans Am Acad Ophthalmol Otolaryngol 1972;76:1462-4.

22. Kiang NYS. An auditory physiologist's view of Menière's syndrome. In: Nadol JB Jr, ed. Second International Symposium on Menière's Disease. Amsterdam: Kugler and Ghedini, 1989 (in press).

23. Arnvig J. Histological findings in a case of Ménière's disease, with remarks on the pathologic-anatomical basis of this lesion. Acta Otolaryngol (Stockh) 1947;35:453-66.

24. Brunner H. Ménière's disease. J Laryngol Otol 1948;62:627-38.

25. Berggren S. Histological investigation of three cases with "Ménière" syndrome. Acta Otolaryngol (Stockh) 1949;37:30-5.

26. Belal A Jr, Ylikoski J. Pathologic significance of Meniere's symptom complex. A histopathologic and electron microscopic study. Am J Otolaryngol 1980;1:275-84.

27. Fraysse BG, Alonso A, House WF. Menière's disease and endolymphatic hydrops. Clinical-histopathological correlations. Ann Otol Rhinol Laryngol 1980;89(suppl 76):2-22.

28. Schuknecht HF, Gulya AJ. Endolymphatic hydrops. An overview and classification. Ann Otol Rhinol Laryngol 1983;92 (suppl 106).

29. Belal A, Antunez JC. Pathology of endolymphatic hydrops. J Laryngol Otol 1980;94:1231-40.

30. Kimura RS, Schuknecht HF. Membranous hydrops in the inner ear of the guinea pig after obliteration of the endolymphatic

sac. Pract Oto-Rhino-Laryngol 1965;27:343-54.

31. Kimura RS. Animal models of endolymphatic hydrops. Am J Otolaryngol 1982;3:447-51.

32. Pearson BW, Brackmann DE. Committee on Hearing and Equilibrium guidelines for reporting treatment results in Meniere's disease [Editorial]. Otolaryngol Head Neck Surg 1985; 93:579-81.

33. Yamashita T, Schuknecht HF. Apical endolymphatic hydrops. Arch Otolaryngol 1982;108:463-6.

34. Landis JR, Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. Biometrics 1977;33:363-74.

35. Schmidt PH. Pathophysiology of the Meniere attack: facts and theories. Acta Otolaryngol (Stockh) 1983;95:417-20.

36. Brown DH, McClure JA, Downar-Zapolski Z. The membrane rupture theory of Meniere's disease — is it valid? Laryngoscope 1988;98:599-601.

37. Torok N. Old and new in Ménière's disease. Laryngoscope 1977;87:1870-7.

38. Silverstein H, Smouha E, Jones R. Natural history vs. surgery for Meniere's disease. Otolaryngol Head Neck Surg 1989; 100:6-16.

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EFFECTS OF UNILATERAL LOSS OF VESTIBULAR FUNCTION ON THE VESTIBULO-OCULAR REFLEX AND POSTURAL CONTROL

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Long-term recovery from surgically induced unilateral loss of vestibular function was studied in 14 patients. Seven patients underwent surgical extirpation or section of the vestibular nerve, and seven patients underwent labyrinthectomy without vestibular nerve section. The vestibulo-ocular reflex (VOR) and postural control were evaluated preoperatively and monitored for up to 4 years postoperatively with use of pseudorandom rotation (combined sinusoidal frequencies from 0.009 to 1.5 Hz) and moving platform posturography. Immediately following surgery all patients showed minimal reductions in the VOR gain constant, but marked reduction in the time constant, and marked increase in slow eye velocity bias. Bias returned to normal values within about 10 days, but time constants never returned to normal values. Results of standard Romberg tests in these patients were normal throughout the preoperative and postoperative periods. However, all patients showed marked postural control abnormalities in tests of the ability to maintain balance in unusual sensory environments in the immediate postoperative period. Seventy-five percent of the patients eventually recovered normal postural control. Postural control returned to near baseline performance with a time course similar to that of the VOR bias. However, postural control also continued to improve after the recovery of VOR bias was complete.

KEY WORDS — acoustic neuroma, Meniere's disease, postural control, vestibular compensation, vestibular function tests, vestibulo-ocular reflex, vestibulo-spinal reflex.

INTRODUCTION

Studies of the vestibulo-ocular reflex (VOR) and postural control following unilateral loss of peripheral vestibular function provide an important means of investigating how the CNS compensates for loss of peripheral sensory information. The VOR and postural control following unilateral peripheral vestibular lesions have been studied extensively, both in animals[1-7] and in humans.[8-15] Following unilateral loss, the gain of the VOR in response to low frequency (less than 0.1 Hz) sinusoidal rotation stimuli is reduced, and phase leads become apparent; gains also become directionally asymmetric, with gains for rotation toward the intact side higher than gains toward the lesioned side.[5,9,11,13] The time constant of the VOR, which reflects the function of the velocity storage mechanism of the central vestibular system,[16] is reduced following unilateral loss of peripheral vestibular function.[5,12] Absolute gain reduction and gain asymmetries have been found to adapt following acute unilateral lesions, but changes in the VOR time constant are permanent. Studies that have employed a large range of test frequencies also have shown that losses in gain at higher rotation frequencies (2 to 3 Hz) occur and can be detected up to 4 years following acute unilateral loss.[14,15] Postural control abnormalities are present immediately following unilateral loss of function in humans and animals,[2-4,8,9] but postural control often appears to recover fully in humans tested with eyes open or closed standing on a firm, immobile surface that provides good somatosensory cues for postural control.[9]

Despite this extensive previous work, many important questions remain to be explored. Many of the studies of the VOR following unilateral lesions have been carried out by use of single frequency sinusoidal rotations (see, for example, Jenkins[12]). Low frequency sinusoidal stimuli (less than 0.1 Hz) assess only the lower range of VOR function, and do not simulate natural head movements very effectively. Of the studies that have employed higher frequency stimuli, most of the assessments have been carried out on patients 6 months or more following the loss of function, and thus have not documented the acute compensatory phase of the recovery.[13-15] Finally, the recovery of postural control following unilateral lesions has not been studied with tests that disrupt the sensory information normally available from both vision and somatosensation.

In order to begin to explore some of these questions, we have studied both the VOR and postural control in 14 patients before and after surgically induced loss of vestibular function. Seven patients underwent surgical extirpation or section of the vestibular nerve, and seven patients underwent labyrinthectomy. The VOR was evaluated with use of a pseudorandom rotation stimulus, which consists of a combination of sinusoidal frequencies ranging from 0.009 to 1.5 Hz. This broad frequency stimulus simulates natural head movements more closely

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TABLE 1. PATIENT CHARACTERISTICS

Patient	*Age*	*Sex*	*Side*	*Diagnosis*	*Observation Period (d)*
Vestibular nerve section					
1	50	M	Left	Meniere's disease	369
2	36	F	Right	Meniere's disease	772
3	47	M	Right	Meniere's disease	197
Acoustic neuroma					
4	50	M	Left	Acoustic neuroma, <1 cm	545
5	33	F	Right	Acoustic neuroma, 2.5 cm	1,603
6	42	F	Left	Acoustic neuroma, 1.5 cm	1,324
7	49	M	Left	Acoustic neuroma, 1.5 cm	370
Labyrinthectomy					
8	41	F	Left	Endolymphatic hydrops	125
9	41	M	Left	Endolymphatic hydrops	97
10	18	F	Left	Endolymphatic hydrops	289
11	65	F	Right	Endolymphatic hydrops	267
12	85	F	Right	Meniere's disease	245
13	64	M	Left	Meniere's disease	875
14	66	F	Right	Cholesteatoma	322

than low frequency single sine rotations. The pseudorandom stimulus appears random to the patient, and is thus more difficult to modify by voluntary effort.[17] Postural control was assessed in the same patients by use of moving platform posturography,[18] which assesses the patient's ability to control sway, both under standard Romberg conditions and in sensory environments lacking reliable visual and/or somatosensory information for postural control. Finally, in order to determine whether the course of recovery is influenced by the presence of residual neural signals from Scarpa's ganglion, the effect of the surgery and the time course of the recovery were compared across patient groups.

METHODS

SUBJECTS

Fourteen patients 18 to 85 years of age participated in this study between August 1983 and March 1988 (Table 1). Patients accepted into this study were screened for signs of unilateral peripheral vestibular dysfunction at the time of surgery; patients with signs of bilateral disease were disqualified. Small unilateral acoustic neuromas arising from the superior branch of the vestibular nerve and not compressing the brain stem were removed from four patients: via a posterior fossa approach in three patients, and via a middle fossa approach in one (patient 6). Three patients with Meniere's disease underwent unilateral vestibular nerve sections via a middle fossa approach. Six patients with endolymphatic hydrops/Meniere's disease and one patient with a cholesteatoma underwent unilateral labyrinthectomy via a transmastoid approach. Thus, a total of seven patients underwent excision or section of the vestibular nerve, and seven patients underwent labyrinthectomy.

PROCEDURE

Design. All patients underwent preoperative evaluations consisting of standard audiometry, standard electronystagmography (including caloric testing at 30°C and 44°C), conventional positional and Hallpike testing, evaluation of saccadic and smooth pursuit eye movements, rotation testing of the VOR, and moving platform posturography. Rotation testing and moving platform posturography are described further below. Preoperative evaluations were completed within 1 month prior to surgery. After the operation, rotation testing and moving platform posturography were repeated (as patient compliance permitted) as soon as possible (usually within 1 week), and at 2 weeks, 1 month, 3 months, 6 months, 1 year, and yearly intervals thereafter. Patients in this study have been observed for periods ranging between 97 days and $4^{1}/_{2}$ years.

Rotation Tests of VOR. Patients were seated in a chair mounted on a 108 N·m velocity servocontrolled motor (Contraves Goerz Corporation model 824) that rotated them about an earth-vertical axis. Horizontal and vertical eye movements were recorded by electro-oculography (EOG) with silver-silver chloride electrodes placed bitemporally and above and below one eye. The EOG calibrations were performed before and after each test. The EOG signals were low pass filtered (0 to 80 Hz) and sampled at 200 Hz (horizontal) and 50 Hz (vertical). Patients were rotated in the dark in a pseudorandom pattern, which consisted of a summation of eight discrete sinusoidal frequencies (0.0092, 0.021, 0.046, 0.095, 0.18, 0.388, and 0.766 Hz with peak velocities of 15°/s, and 1.535 Hz with peak velocities of 7.8°/s). The highest instantaneous velocity of the pseudorandom stimulus was about 80°/s. During each test, patients were given mental tasks to maintain alertness. Stimulus delivery and data collection were controlled by a DEC LSI 11/73 computer.

The EOG data were digitally filtered and differentiated to produce eye velocity, and fast phase eye movements were detected by a velocity threshold calculation and eliminated from the data record (procedure similar to that described by Barnes[19]). For data from pseudorandom rotations, Fourier analyses were performed for both the slow eye movement velocity records and the chair velocity records. The VOR gain measures were derived by calculation of the ratio of the amplitudes of the Fourier components of the eye velocity to the chair velocity. Response phases (in degrees) were calculated from the Fourier components of the chair velocity and the slow eye velocity. Phase values represent the time shift of the slow eye velocity relative to

TABLE 2. SENSORY TESTS OF POSTURAL CONTROL

Condition	*Visual Surround*	*Platform*	*Normal Sensory Feedback*	*Abnormal Sensory Feedback*
1	Fixed	Fixed	Vestibular, somatosensory, visual	
2	Eyes closed	Fixed	Vestibular, somatosensory	
3	Sway-referenced	Fixed	Vestibular, somatosensory	Visual
4	Fixed	Sway-referenced	Vestibular, visual	Somatosensory
5	Eyes closed	Sway-referenced	Vestibular	Somatosensory
6	Sway-referenced	Sway-referenced	Vestibular	Visual, somatosensory

the chair velocity. In the convention used here, a response with unity gain and zero phase represents a perfectly compensatory eye movement. In order to estimate the time constant of the VOR, the gain and phase values for the pseudorandom stimulus were plotted as a function of stimulus frequency, and the data were fitted with a transfer function equation of the following form:

$$H_{vor}(s) = \frac{K_V T_V s}{T_V s + 1}$$

where Tv is an estimate of the VOR time constant (in seconds), Kv is the VOR gain constant, and s is the Laplace transform variable. The VOR bias (average slow phase eye velocity over the duration of the stimulus) also was calculated. Patient data were compared to those of 216 normal subjects ranging in age from 7 to 81 years who were tested with the same equipment and protocol.[20]

Moving Platform Posturography. The postural control tests used in these studies have been described in detail elsewhere.[18] Patients stood on a hydraulically driven platform that could be translated horizontally forward or backward or rotated about an axis co-linear with the patients' ankle joints. Patients faced into a styrofoam enclosure that surrounded them on three sides and was open at the back. The surface of the enclosure was painted white and covered with a pattern of randomly spaced colored dots. This enclosure filled the patients' visual field, and also could be rotated about the patients' ankle joints. During testing, subjects wore a modified parachute harness attached to the ceiling to prevent injury from a fall. Body sway was measured with a potentiometer attached to the patients' hips by a system of lightweight rods. Platform and visual surround movement and data collection were controlled by a DEC LSI 11/23 computer. Sway data were sampled at 50 Hz and stored for off-line analysis.

Patients underwent two tests of postural control. For tests of *motor control*, muscle onset patterns and latencies and body sway in response to forward and backward horizontal translations (3 cm at 12 cm/s) and toe-up and toe-down rotations (5° at 20°/s) of the platform were recorded. Data for all patients tested at all times preoperatively and postoperatively were within normal limits established for 216 healthy subjects,[20] and therefore these results are not presented here. In tests of *sensory organization*, the patients' ability to use visual, vestibular, and somatosensory information to control sway in unusual sensory environments was assessed. The patients' task was to stand with as little sway as possible for 21 seconds in each of six different conditions (see Table 2 for a summary of experimental conditions). In conditions 1 and 2, the patients stood on the fixed platform facing into the fixed visual surround, first with eyes open (condition 1) and then with eyes closed (condition 2). This test is equivalent to the standard Romberg test.

In the remaining four test conditions, sensory information from the visual and/or somatosensory systems was altered systematically by "sway-referencing" the visual surround and/or the platform. During sway-referenced conditions, the platform and/or the visual surround were rotated in the same direction as and in exact proportion to the patients' sway (ie, forward sway produces toe-down rotation of the platform and/or forward rotation of the visual surround). Under these conditions, the movement of the visual surround's image on the retina, ankle position, and the position of the center of pressure on the feet no longer relate to the position of the center of gravity as they do under normal circumstances. For condition 3, only the visual surround was sway-referenced, and in condition 4, only the platform was sway-referenced. In condition 5, the patients stood on the sway-referenced platform with eyes closed, and in condition 6 both the platform and the visual surround were sway-referenced. During the first second of each trial, both the platform and the visual surround were held fixed to permit recording of baseline measures.

Peak-to-peak sway amplitude was calculated from the hip position trace for each trial. Sway was judged abnormal if the patient fell, if the patient was forced to take a step, or if the amplitude of the subject's sway exceeded the 95th percentile limits for a population of 216 normal subjects tested by the same protocol and equipment.[20] The majority of the patients received one trial in each condition; some patients, however, received up to three trials in conditions 3 through 6. In these cases, performance on the first trial only is reported in order to permit valid comparisons of the performance of different patients.

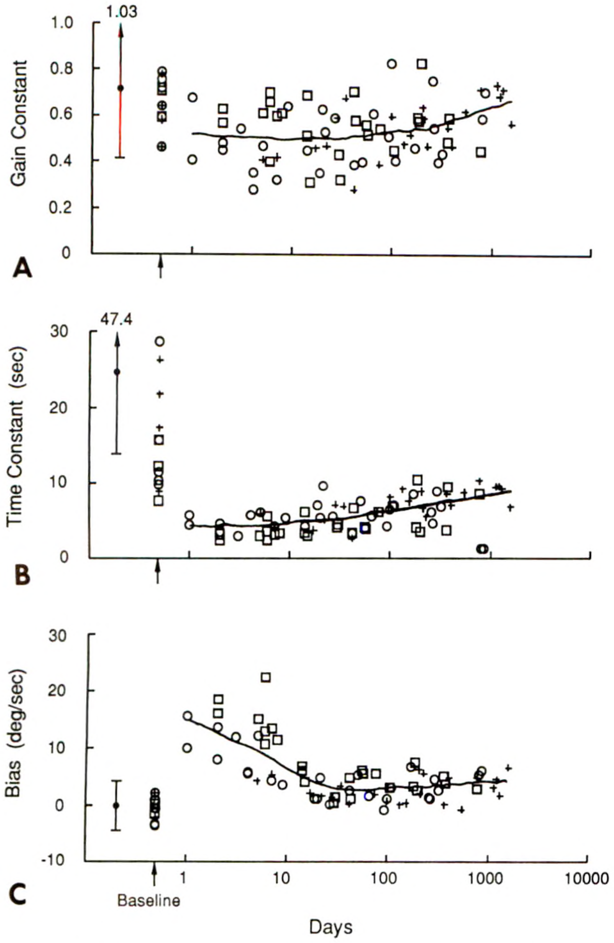

Fig 1. Results of pseudorandom rotation testing. A) Gain constant, B) time constant, and C) bias are plotted as function of time in days following surgical procedure (logarithmic scale). Baseline (preoperative) values are plotted to left of postoperative data, and are indicated by arrow on abscissa. Mean and 95th percentile ranges for 216 normal subjects are shown by vertical line to left of preoperative values. Curve fits to scattered data were made by means of weighted least squares regression (LOWESS). Patients with acoustic neuromas, + ; patients with vestibular nerve sections, □; patients with labyrinthectomies, ○.

RESULTS

VOR in Response to Pseudorandom Rotations. The results for the pseudorandom rotations are plotted in Fig 1. For all panels in Fig 1, time in days following surgery is plotted on a logarithmic scale on the abscissa. Baseline (preoperative) values are plotted to the left of the postoperative data, and indicated by the arrow on the abscissa. The vertical line to the left of the baseline values indicates the 95th percentile range of values for normal subjects, and the solid dot indicates the mean of these values. The values for our normal population closely parallel those previously reported by Jenkins[12] for similar stimulus ranges. The top panel shows the VOR gain constant plotted as a function of time; the middle shows the VOR time constant, and the bottom panel shows the bias, or average slow phase eye velocity for the duration of the stimulus. Positive bias values indicate that the average velocity was directed away from the normal ear. In all panels, a curve has been fitted to the postoperative data by the LOWESS method.[21,22] The LOWESS method fits a curve to scattered data by use of a locally weighted least squares technique. Curves generated in this manner can be fitted validly to scatterplots with either linear or nonlinear trends. The LOWESS curves also are weighted to de-emphasize outliers, and are therefore relatively insensitive to extreme data points.

The preoperative values and the postoperative course of recovery were highly similar for all three surgical groups. The preoperative values of the VOR gain constant were within normal limits for all patients, and declined minimally following surgery. The majority of patients still had gain constant values within normal limits even during the immediate postoperative period, and all patients had gain constants within normal limits at about 3 months postoperatively. The LOWESS regression curve shows a flat recovery course for the VOR gain constant. The VOR time constants were below normal limits in about half the patients prior to surgery, but regardless of their preoperative status, all patients showed marked reductions in the VOR time constant postoperatively. Time constants in the immediate postoperative period were at or below presumptive vestibular nerve time constant levels (5 to 7 seconds). The postoperative reductions in the VOR time constant are apparently permanent. Although time constants increased slowly in the postoperative period, they never regained normal levels. Bias values preoperatively were within normal limits and scattered about zero. In the immediate postoperative period, all patients tested had high positive values, which recovered within about 10 days to the upper range of normal values. Subsequent changes in bias were minimal.

Moving Platform Posturography. Figure 2 shows the proportion of abnormal trials at preoperative testing and three postoperative intervals in each sensory condition. (Refer to Table 2 for a summary of the sensory information available in each condition.) The postoperative period was divided into three periods (0 to 9 days, 10 to 99 days, and 100 to 999 days) representing equal logarithmic divisions. Not all patients agreed to testing in each interval; all 14 patients were tested prior to the operation, ten patients were tested at least once in the interval 0 to 9 days, 13 patients were tested at least once during the interval 10 to 99 days, and 13 patients were tested at least once during the interval 100 to 999 days. The patients who were not tested during the 0- to 9-day interval refused testing because of pronounced symptoms of fatigue and unsteadiness that appeared to be residual effects of anesthesia. For patients tested repeatedly within a given interval, results are plotted for the first test within that interval only. The median number of postoperative

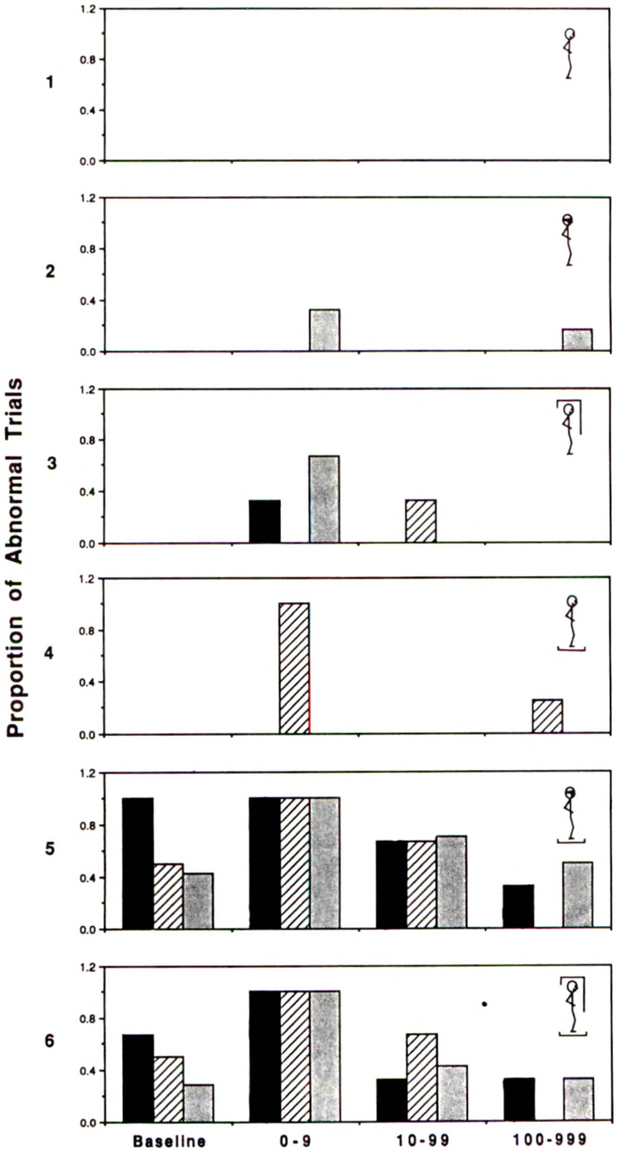

Fig 2. Proportion of abnormal posturography trials in each of six sensory conditions (refer to Table 2) preoperatively and at three selected postoperative intervals. Numbers 1 through 6 to left of ordinates in each panel and stick figures in upper right corner of each panel indicate sensory condition. Blindfolds — eyes closed, box around head — sway-referenced vision, box around feet — sway-referenced platform, dark bars — patients with vestibular nerve sections, hatched bars — patients with acoustic neuromas, stippled bars — patients with labyrinthectomies.

days at testing for each interval was 2 for the period labeled 0 to 9, 21 for the period labeled 10 to 99, and 188 for the period labeled 100 to 999.

Results are again similar for all surgical groups. Almost all patients swayed within normal limits in conditions 1 and 2 (equivalent to the standard clinical Romberg test) at all times before and after the operation. Prior to the operation, 36% of the patients swayed excessively or fell in conditions with both abnormal visual and abnormal somatosensory feedback (conditions 5 and 6). Only 5% of the normal population fell in the same conditions. In the immediate postoperative period, all patients tested swayed excessively or fell in conditions 5 and 6. Six (60%) patients also swayed excessively or fell in either condition 3 (abnormal visual feedback only; five patients) or condition 4 (abnormal somatosensory feedback only; one patient). Recovery of postural control was rapid; roughly the same proportion of patients showed significant postural abnormalities preoperatively and at the 10- to 99-day interval. Five patients (1, 2, 5, 12, and 14) showed abnormalities in both conditions 5 and 6 preoperatively, and six patients (1, 4, 6, 12, 13, and 14) showed abnormalities in the same conditions at the 10- to 99-day interval. However, postural control, unlike the VOR measures, continued to improve slightly at even longer postoperative intervals. Only three patients (2, 12, and 13) showed abnormalities in both conditions 5 and 6 at the 100- to 999-day interval.

DISCUSSION

As has been shown previously for animals like the rat,[7] the results of these studies indicate that preservation of Scarpa's ganglion appears to have little if any effect on VOR or postural control compensation for unilateral loss of vestibular function. For all groups, the most dramatic change in vestibulo-ocular function during the acute phase of compensation following unilateral loss of vestibular function occurred during the first 10 postoperative days, as the VOR bias returned quickly to values near the normal preoperative baseline. The VOR response amplitude (gain constant) for the pseudorandom stimulus was affected minimally by the surgical procedure. In marked contrast, time constants decreased following unilateral loss of vestibular function and did not recover to normal ranges for as long as 4 years postoperatively. This permanent disruption of the brain stem velocity storage mechanism[16] has been demonstrated previously in both animals[5] and humans[11,12] following labyrinthectomy and vestibular nerve section.

The time course of the recovery of postural control was also highly similar for all patient groups. Approximately one third of the patients fell or swayed excessively in conditions with unreliable visual and somatosensory feedback for postural control prior to the operation. During the immediate postoperative period, however, all of the patients who could be tested showed postural control abnormalities in the same conditions. In addition, two thirds of the patients also showed abnormalities in other conditions, in which either somatosensory information (condition 3) or visual information (condition 4) was available and reliable. The inability of some patients to control posture in conditions 3 and 4 disappeared within 2 to 3 weeks of the operation, and residual postural control abnormalities occurred almost exclusively in conditions 5 and 6, which require vestibular information to maintain balance.

At approximately 6 months following the operation, three fourths of the patients had recovered normal postural control.

The means by which the CNS regains relatively normal vestibulo-ocular function and postural control are not completely understood. Recent studies of VOR compensation for unilateral loss of function indicate that several different mechanisms may be used.[13,14,23] Tests of visual-vestibular interactions have shown that patients who have sustained sudden unilateral loss of function may 1) improve vestibulo-ocular function by using visual or somatosensory information when available, 2) may use prediction or voluntary enhancement of the VOR, or 3) may show adaptive gain changes in the VOR. Some of the same mechanisms also may be available to the postural control system. Studies of the responses of monkeys with unilateral labyrinthectomies to sudden falls have shown that in the immediate postoperative period, these animals required visual information to organize a timely postural response. Later in compensation, visual information was no longer necessary. Similar behavior was observed in the patients studied here. During the acute recovery phase, five of ten patients fell when exposed to the sway-referenced visual surround, as though they had become highly dependent on visual information for the control of posture. It is possible that animals and humans rely heavily on other sensory systems for oculomotor and postural control during the acute recovery phase, and that adaptive changes in the vestibular system itself occur later.

REFERENCES

1. Wolfe JW, Kos CM. Nystagmus responses of the rhesus monkey to rotational stimulation following unilateral labyrinthectomy: final report. Trans Am Acad Ophthalmol Otolaryngol 1977;84:ORL38-ORL45.

2. Lacour M, Xerri C, Hugon M. Compensation of postural reactions to fall in the vestibular neurectomized monkey: role of the remaining labyrinthine afferences. Exp Brain Res 1979;37:563-80.

3. Lacour M, Xerri C. Vestibular compensation: new perspectives. In: Flohr H, Precht W, eds. Lesion-induced neuronal plasticity in sensorimotor systems. Berlin: Springer Verlag, 1981:240-53.

4. Ishikawa K, Igarashi M, Yoshihara T. Post-labyrinthectomy balance compensation influenced by pre-placement of descending medial longitudinal fasciculus lesion. Acta Otolaryngol (Stockh) 1986;102:118-23.

5. Fetter M, Zee DS. Recovery from unilateral labyrinthectomy in rhesus monkey. J Neurophysiol 1988;59:370-93.

6. Maioli C, Precht W, Ried S. Short- and long-term modifications of vestibulo-ocular response dynamics following unilateral vestibular nerve lesions in the cat. Exp Brain Res 1983;50:259-74.

7. Sirkin DW, Precht W, Courjon J-H. Initial rapid phase of recovery from unilateral vestibular lesion in rat not dependent on survival of central portion of vestibular nerve. Brain Res 1984;302:245-56.

8. Schaefer K-P, Meyer DL. Compensation of vestibular lesions. In: Kornhuber H, ed. Vestibular system, part 2. Psychophysics, applied aspects and general interpretation. Berlin: Springer, 1974:463-90. (Handbook of sensory physiology; vol 8).

9. Fregly AR. Vestibular ataxia and its measurement in man. In: Kornhuber H, ed. Vestibular system, part 2. Psychophysics, applied aspects and general interpretation. Berlin: Springer, 1974:321-60. (Handbook of sensory physiology; vol 8).

10. Olson JE, Wolfe JW, Engelken EJ. Responses to low-frequency harmonic acceleration in patients with acoustic neuromas. Laryngoscope 1981;91:1270-7.

11. Honrubia V, Jenkins HA, Baloh R, Yee RD, Lau CGY. Vestibulo-ocular reflexes in peripheral labyrinthine lesions: I. Unilateral dysfunction. Am J Otolaryngol 1984;5:15-26.

12. Jenkins HA. Long-term adaptive changes of the vestibulo-ocular reflex in patients following acoustic neuroma surgery. Laryngoscope 1985;95:1224-34.

13. Hart CW, McKinley PA, Peterson BW. Compensation following acute unilateral total loss of peripheral vestibular function. In: Graham MD, Kemink JL, eds. The vestibular system: neurophysiologic and clinical research. New York: Raven Press, 1987:187-92.

14. Ödkvist LM, Möller CG, Larsby B, Hydén D. Vestibular compensation measured by the broad frequency band rotatory test. In: Graham MD, Kemink JL, eds. The vestibular system: neurophysiologic and clinical research. New York: Raven Press, 1987:287-91.

15. Hydén D, Larsby B, Möller C, Ödkvist L, Ekvall L. Rotatory and caloric findings in patients with acoustic neuromas. In: Graham MD, Kemink JL, eds. The vestibular system: neurophysiologic and clinical research. New York: Raven Press, 1987:351-7.

16. Raphan T, Matsuo V, Cohen B. Velocity storage in the vestibulo-ocular reflex arc (VOR). Exp Brain Res 1979;35:229-48.

17. Barr CC, Schultheis LW, Robinson DA. Voluntary, non-visual control of the human vestibulo-ocular reflex. Acta Otolaryngol (Stockh) 1976;81:365-75.

18. Nashner LM, Black FO, Wall C. Adaptation to altered support surface and visual conditions during stance: patients with vestibular deficits. J Neurosci 1982;2:536-44.

19. Barnes GR. A procedure for the analysis of nystagmus and other eye movements. Aviat Space Environ Med 1982;53:676-82.

20. Peterka RJ, Black FO. Normal and abnormal vestibular function: final technical report. NASA Cooperative Agreement NCC9-8, 1986.

21. Cleveland WS. Robust locally weighted regression and smoothing scatter plots. J Am Stat Assoc 1979;74:829-36.

22. Chambers JM, Cleveland WS, Kleiner B, Tukey PA. Graphical methods for data analysis. Boston: Duxbury Press, 1983:91-104.

23. Watt DGD, Peterson B. Recovery from peripheral vestibular defects: VOR and VSR. In: Barber HO, Sharpe A, eds. Vestibular disorders. Boca Raton, Fla: CRC Press, 1989:35-47.

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TOTAL CERVICAL TRACHEAL STENOSIS: TREATMENT BY LASER, DILATION, AND STENTING

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Twelve patients with total cervical tracheal stenosis were treated by endoscopic laser excision (neodymium:yttrium aluminum garnet or carbon dioxide laser), bronchoscopic dilation, and prolonged stenting with a silicone T-tube. All patients had previous traumatic or prolonged endotracheal intubation requiring a tracheotomy and presented with aphonia as the major complaint. Multiple laser and dilation treatments were necessary in ten patients. Average duration of T-tube placement was 6 months. Excellent results (decannulation and good voice) were achieved in eight patients with a follow-up of 9 months to 6 years. Persistent granulation tissue and some degree of fibrosis were the most common complications (eight of 12 patients). Two patients died of medical complications. A high success rate with this endoscopic technique justifies this approach as our initial therapy, with open surgical techniques reserved for failure.

KEY WORDS — bronchoscopic dilation, carbon dioxide laser, complete tracheal stenosis, endoscopic excision, neodymium:yttrium aluminum garnet laser, silicone T-tube, stenting.

INTRODUCTION

Total cervical tracheal stenosis is usually a complication of prolonged endotracheal intubation or traumatic intubation in an emergency setting, with subsequent subglottic or tracheal stenosis occurring secondary to granulation tissue and ultimately fibrosis. Patients with complete obstruction of the cervical trachea are dependent on their tracheotomy as the only airway and are aphonic. Options in management include an open surgical approach, namely, tracheal resection and reanastomosis; external tracheoplasty using graft material and possible stenting; and endoscopic incision or excision of scar tissue, dilation, and stenting.

Endoscopic treatment of tracheal stenosis using the carbon dioxide laser through a laryngoscopic or bronchoscopic approach or both has been reported by a number of authors with varying success. Simpson et al,[1] using prototypic first-generation CO_2 laser instrumentation, presented their series of 60 patients with laryngeal (49 patients), tracheal (six patients), and combined laryngeal and tracheal stenosis (five patients). Successful management was noted with use of multiple procedures in 35 patients. Patients with tracheal stenosis had a higher failure rate, requiring subsequent open surgical procedures. Factors generally associated with poor results included circumferential scarring with contracture, scarring greater than 1 cm in the vertical dimension, a previous history of severe bacterial infection associated with tracheotomy, loss of cartilage or tracheomalacia, and scarring of the posterior glottic airway, often with arytenoid fixation. Other authors, such as Koufman et al[2] and Ossoff et al,[3] reported generally favorable success rates: 77% for subglottic stenosis and 57% for tracheal stenosis, respectively. To improve the somewhat disappointing success rate with use of the CO_2 laser for endoscopic management of subglottic and tracheal stenosis, Dedo and Sooy[4] reported the use of a "microtrapdoor" flap in the posterior glottic region for posterior glottic stenosis and weblike tracheal stenosis. The CO_2 laser was used to elevate this flap of epithelium, permitting vaporization of underlying scar tissue with the laser. The epithelial flap then was placed back into position for reepithelialization of the wound. Eight of nine patients treated in this fashion had successful outcomes.

The major limitation in the endoscopic management of tracheal stenosis appeared to be related to the disease process itself rather than the instrumentation. Weblike or fibrous stenoses were associated with a high success rate as opposed to the higher degree of failure associated with collapsing cartilage or tracheomalacia. This latter condition should be treated by tracheal resection and reanastomosis as the primary treatment. Long-term stenting of collapsing tracheal cartilage was reported by Montgomery[5] in 1965, using a silicone tracheal T-tube. This technique proved to be most useful in patients who were not considered candidates for open external surgical procedures. Shapshay et al[6] stressed the use of radial laser incisions with either the CO_2 laser or a contact neodymium:yttrium aluminum garnet probe followed by gentle dilation with use of the bronchoscope in a rotational axis without stenting.

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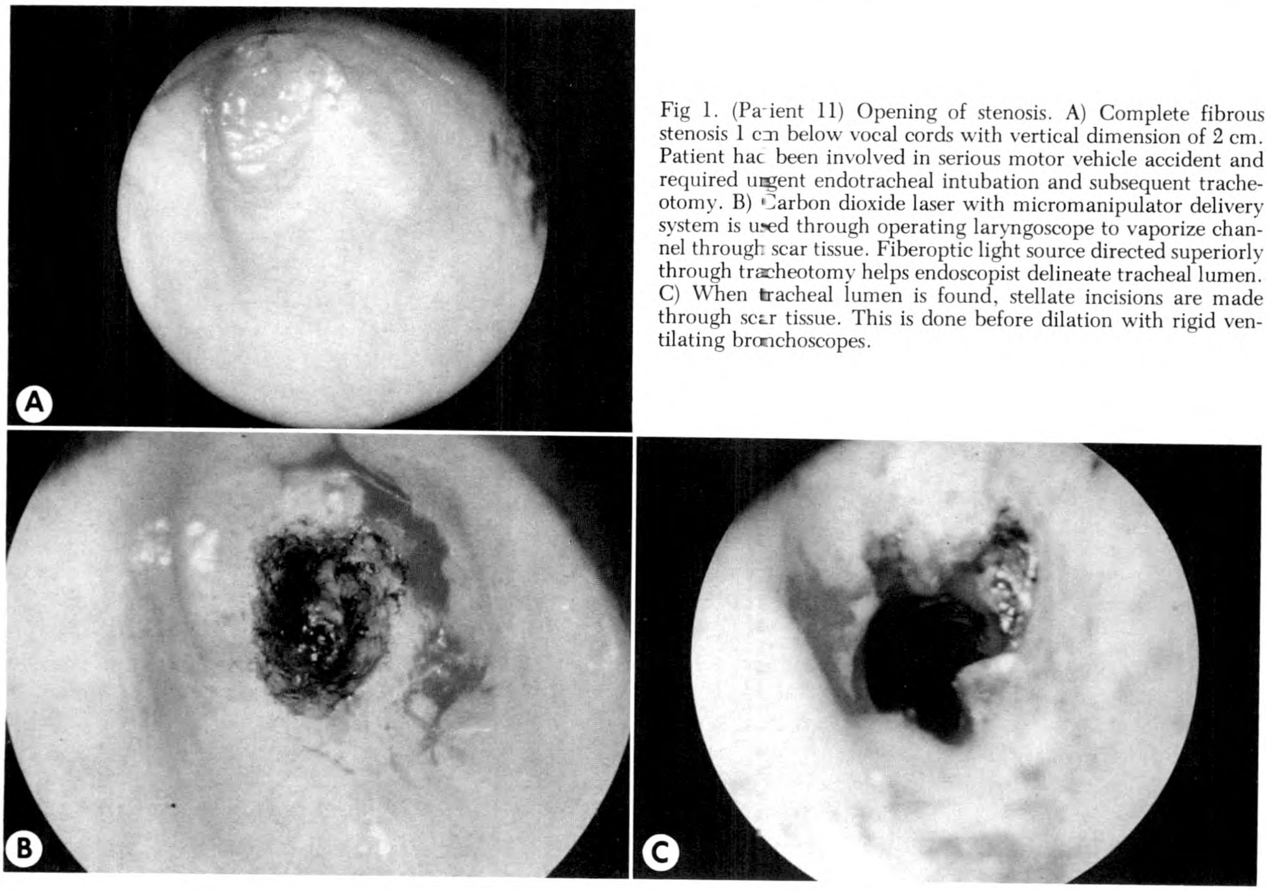

Fig 1. (Patient 11) Opening of stenosis. A) Complete fibrous stenosis 1 cm below vocal cords with vertical dimension of 2 cm. Patient had been involved in serious motor vehicle accident and required urgent endotracheal intubation and subsequent tracheotomy. B) Carbon dioxide laser with micromanipulator delivery system is used through operating laryngoscope to vaporize channel through scar tissue. Fiberoptic light source directed superiorly through tracheotomy helps endoscopist delineate tracheal lumen. C) When tracheal lumen is found, stellate incisions are made through scar tissue. This is done before dilation with rigid ventilating bronchoscopes.

A high degree of success was achieved in carefully selected patients with intraluminal fibrous stenosis without tracheal collapse. The rationale behind this technique was to preserve islands of epithelium between the radial laser incisions, which could rapidly reepithelialize the tracheal wall. A successful outcome usually ensued if epithelialization was complete within 3 to 4 weeks.

This paper presents our experience with 12 patients with use of CO_2 and Nd:YAG laser technology through both laryngoscopic and bronchoscopic exposures for incision or excision or both, dilation, and prolonged stenting of complete strictures of the subglottic and cervical trachea. Prolonged stenting, usually for 6 months, was accomplished with a silicone T-tube.

MATERIALS

The Nd:YAG laser used in nine patients was a 100-W continuous wave laser produced by Cilas (Biolas YAG 100; Cilas Co, Marcousis, France) used with a standard quartz 2.3-mm fiber. The laser was delivered through a rigid bronchoscope system designed by Dr Jean-Francois Dumon (Marseille, France) and Dr James Harrell (University of California San Diego Medical Center) for Nd:YAG laser application and simultaneous use of 0° telescopic optics. This bronchoscope features special external channels for insertion of the laser fiber and one or two suction catheters for removal of debris and secretions (Bryan Corp, Woburn, Mass). Average power settings of 30 W at 0.7-second exposures were used, with the laser fiber kept close to the target tissue (2 mm). The CO_2 laser system was a 40-W continuous wave laser made by Heraeus LaserSonics, Inc (Merrimack ML 840, Milpitas, Calif) delivered through a microscopic manipulator. The microscopic manipulator was coupled to a Zeiss operating microscope with a 400-mm lens (Fig 1). The patients were kept under general anesthesia by use of an endotracheal tube through the tracheotomy site. After laser treatment of the stenotic area, rigid bronchoscopy (Karl Storz Endoscopy-America Inc, Culver City, Calif) was performed to dilate carefully the stenotic region. The trachea was dilated with first a 7.5-mm and next an 8.5-mm rigid ventilating bronchoscope and a Venturi jet oxygenation system. After the laser treatment and dilation, an adult size, 12- to 14-mm silicone T-tube (Boston Medical Products, Inc, Waltham, Mass) was used (Figs 2 and 3).

A useful technique to facilitate precise laser excision of the tracheal scar tissue was the use of a flexible fiberoptic bronchoscope through the tracheotomy site aimed superiorly. With the light somewhat dimmed in the operating room, the scar tissue could be transilluminated to guide the endoscopist safely through the tracheal lumen, avoiding injury to the tracheal cartilage. After operation, the patients re-

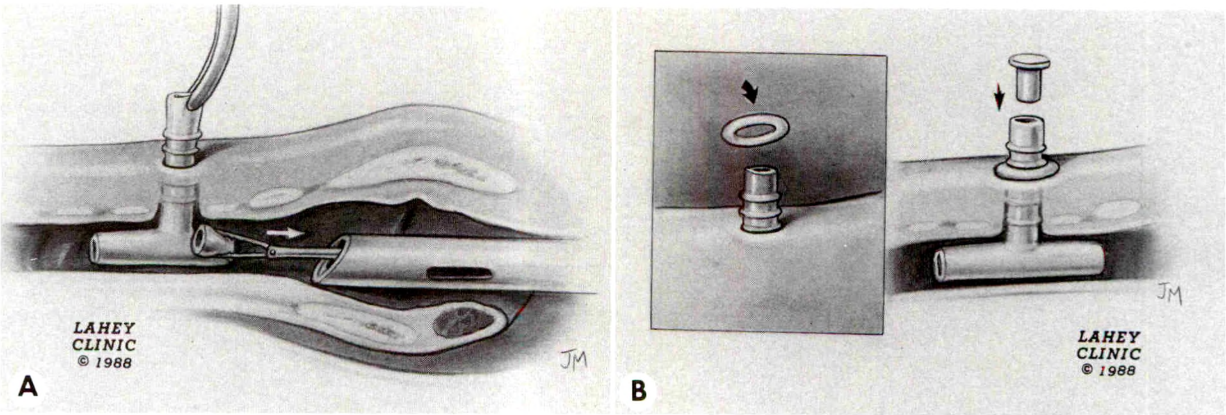

Fig 2. Placement of silicone T-tube. A) Tube being placed through tracheotomy site by use of rigid bronchoscope and forceps to aid in positioning. It is important to have T-tube stent stenotic area without traumatizing vocal cords. B) Tube in place with safety ring applied to prevent tube displacement. It is important to keep T-tube plugged to prevent drying of secretions and subsequent crust formation.

ceived a broad-spectrum antibiotic for 10 days. Steroids were avoided for fear of causing a delay in epithelial migration. Care was taken to plug the T-tube externally as soon as the patient was fully awake from anesthesia. Further postoperative management consisted of humidified oxygen in the recovery room, careful suctioning at least four times daily, administration of sterile normal saline and acetylcysteine (Mucomyst, 10%), and careful cleansing of the inside of the T-tube with cotton-tipped applicators dipped in hydrogen peroxide. Further instructions were given to the patient according to guidelines reported by Montgomery.[7]

PATIENTS

Twelve patients with complete subglottic or cervical tracheal stenoses (see Table) were treated from 1981 to 1988 at the Lahey Clinic Medical Center, Burlington, Mass (three patients), and the Salvator Hospital, Marseille, France (nine patients). Eight patients were men and four patients were women in this series, with a median age of 45.5 years (range, 19 to 72 years). A common denominator in the cause of their tracheal stenosis was urgent endotracheal intubation for treatment of motor vehicle accident trauma (seven patients) or a suicide attempt (two patients); or prolonged intubation subsequent to cardiac surgery (one patient), acute myocardial infarction with cardiac arrest (one patient), or respiratory insufficiency secondary to a cerebrovascular accident (one patient). These patients underwent tracheotomy because endotracheal tube extubation could not be completed successfully. All of these patients were aphonic as a result of complete tracheal stenosis between the tracheotomy site and the vocal cords (Fig 1A). The vertical dimension of the stenoses ranged from 1 to 3 cm. Tracheal tomography was performed on all patients to ascertain the integrity of the tracheal cartilages.

Nine patients were treated with the Nd:YAG laser and three patients with the CO_2 laser. Ten of 12 patients required multiple laser and dilation treatments. Three patients had two treatments over 12 months, one patient (patient 1) had four treatments over 2 years, and another (patient 8) had five treatments over 3 years for the removal of granula-

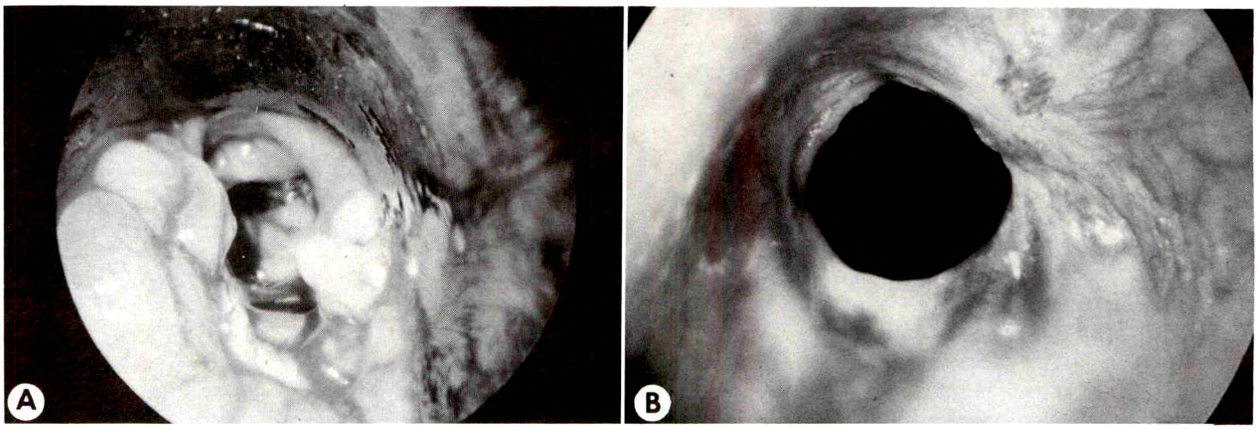

Fig 3. (Patient 11) A) At time of T-tube removal, 6 months after laser treatment and stenting. Note moderate amount of granulation tissue in trachea, which was removed with CO_2 laser. Tracheal decannulation was achieved. B) Three months after stent removal. Diameter of lumen is 6 mm. Further laser treatment and dilation were performed to establish 9-mm tracheal lumen.

PATIENTS WITH TOTAL TRACHEAL STENOSIS

Patient	*Age (yr)*	*Sex*	*Cause of Stenosis*	*Treatment*	*Post-T-Tube Therapy*	*Results of Endoscopic Therapy*	*Follow-Up (yr)*
1	35	M	Intubation trauma (MVA)	Nd:YAG laser, dilation, T-tube (2 mo)	Nd:YAG laser x4 (granulation, fibrosis)	Excellent	2
2	49	M	Intubation trauma (MVA)	Nd:YAG laser, dilation, T-tube (6 mo)	Nd:YAG laser x2 (granulation)	Good	1*
3	50	F	Intubation trauma (suicide)	Nd:YAG laser, dilation, T-tube (4 mo)	Nd:YAG laser x1 (fibrosis), sleeve resection 2 mo later	Poor (with T-tube)	6
4	34	M	Intubation trauma (MVA)	Nd:YAG laser, dilation, T-tube (8 mo)	Nd:YAG laser x1	Excellent	4
5	45	M	Intubation trauma (MVA)	Nd:YAG laser, dilation, T-tube (14 mo)	None	Excellent	1
6	72	M	Prolonged intubation after cardiac surgery	Nd:YAG laser, dilation, T-tube (6 mo)	Nd:YAG laser x2 (granulation)	Excellent	5
7	52	M	Intubation trauma (MVA)	Nd:YAG laser, dilation, T-tube (6 mo)	Sleeve resection, Nd:YAG laser x4	Poor	5
8	19	F	Intubation trauma (MVA)	Nd:YAG laser, dilation, T-tube (6 mo)	Nd:YAG laser x5 over 3 yr	Fair with T-tube; final, excellent	5
9	27	F	Intubation trauma (suicide)	Nd:YAG laser, dilation, T-tube (12 mo)	Nd:YAG laser x2 over 6 mo	Excellent	2
10	46	M	Intubation trauma (MI, cardiac arrest)	CO_2 laser, dilation x3, T-tube x2 (6 mo)	CO_2 laser removal of granulation	Excellent	9 mo†
11	23	M	Intubation trauma (MVA)	CO_2 laser, dilation, T-tube (6 mo)	None	Excellent	1
12	65	F	Prolonged intubation (CVA, COPD)	CO_2 laser, dilation x2, T-tube (3 mo)	Tracheal cannula	Poor	18 mo

MVA — motor vehicle accident, MI — myocardial infarction, CVA — cerebrovascular accident, COPD — chronic obstructive pulmonary disease.

*Died of tuberculosis.

†Died of myocardial infarction at decannulation.

tion tissue and recurrent fibrosis. T-tube placement ranged from 2 to 14 months, with the average duration being 6 months.

RESULTS

An excellent therapeutic result was considered to be tracheotomy decannulation, near-normal voice, and normal respiratory function with good exercise tolerance. According to these criteria, eight patients in our series had excellent results, with follow-up ranging from 9 months to 6 years (see Table). One patient (patient 10) died of an acute myocardial infarction at the time of decannulation with an excellent airway. In one patient (patient 2), granulation tissue persisted despite endoscopic therapy. This was considered to be a good result with regard to extubation of the tracheotomy, but intermittent persistent granulation caused mild airway distress. This patient actually had acute tuberculosis and died of this disease process 1 year after beginning endoscopic therapy. Three patients had poor results from endoscopic therapy, and two (patients 3 and 7) underwent sleeve resection of the trachea with a final good result. Laser therapy was helpful in one of these patients (patient 7) in treating granulation tissue on the anastomosis line after tracheal resection. Only one patient (patient 12) failed to tolerate T-tube placement because of poor compliance with postoperative management instructions. This patient had had a severe cerebrovascular accident necessitating intermittent respiratory support through a tracheotomy cannula.

Neither the use of the laser nor dilation resulted in tracheal perforation. Postoperative neck and oral pharyngeal discomfort were transient symptoms for the first 24 to 48 hours. No complications with the use of the laser were noted, ie, endotracheal fires or burns. The absence of infection was noteworthy in this series of patients. Persistent granulation tissue and some degree of fibrosis were the most common complications (eight of 12 patients). Only one of these patients, however, required a permanent tracheotomy and was considered a failure of therapy (patient 12).

DISCUSSION

As mentioned previously, the common denominator in the cause of total cervical tracheal stenosis is traumatic intubation causing an injury in the subglottic or cervical trachea, which progresses to form cicatricial fibrosis. This condition is to be considered a complex tracheal stenosis with granulation tissue, fibrosis, and some element of tracheal wall collapse. Most of the patients in this series had a medical emergency, whether motor vehicle accident trauma, a suicide attempt, cardiac arrest, or acute respiratory insufficiency from chronic obstructive pulmonary disease. Endotracheal intubation was done on an urgent basis and in some instances perhaps by the most inexperienced member of the health care team. Often the endotracheal tube was left in place for a prolonged period (longer than 2 weeks) before tracheotomy. Some of these patients were on prolonged respiratory support, adding another element of risk, namely, constant movement of the inflated endotracheal tube cuff excoriating the tracheal mucosa.

Options in management of total tracheal stenosis include endoscopic techniques and open surgical procedures. The inherent advantage of endoscopic treatment is potentially lessened morbidity compared with that of open surgical procedures. This advantage would apply particularly to older patients with high medical risk factors, such as diabetes, chronic obstructive pulmonary disease, and cardiovascular disorders. Endoscopic therapy, of course, does not preclude future open resection and in fact may facilitate tracheotomy extubation, removing a potential source of infection before open surgery. If an open surgical procedure is chosen, it would appear that a tracheal sleeve resection and reanastomosis, if technically possible, would be the most efficient procedure. Most tracheal surgeons would prefer to do this operation without the presence of a preexisting tracheotomy.

The use of stenting materials in the trachea has been a source of controversy. If a stent is used, it should be made of an inert material that does not become a source of infection while in place. The ideal tracheal stent should fit the tracheal lumen snugly and in fact provide some expansion of a narrowed tracheal wall. A stent that is too small can become displaced, causing airway obstruction, and because of movement can become a source of chronic irritation and subsequent infection. The tracheal stent also should be easy to clean and made of material that does not stimulate increased secretions. Secretions in general should not become easily adherent to the inner lumen of the tube.

In 1965, Montgomery[5] introduced a silicone rubber T-tube for the relief of subglottic stenosis, and this tube subsequently has been modified with grooves on the external limb of the T-tube, providing a safer tube with less chance of displacement.[7] We have found that a silicone rubber prosthesis may be left in the trachea for 12 months or more without any adverse reaction. A modification of this T-tube design has been reported by Westaby et al,[8] who created a bifurcated silicone rubber stent to intubate the trachea and main bronchi. This stent was designed to palliate intrathoracic tracheal compression by a neoplastic process as well as unresectable tracheal stenosis. Placement of this stent is through the tracheotomy with use of guide wires to direct the stent into the main bronchi proximally. A modification of the T-tube design, reported by Duvall and Bauer,[9] permits insertion of a more flexible stent under direct vision through the larynx over a bronchoscope.

An expandable stainless steel stent originally used in vascular stenosis was modified for tracheobronchial use by Wallace et al.[10] This springlike, expandable metallic stent was applied in the trachea and bronchi of 11 healthy dogs, expanding gradually over time and substantially increasing the diameter of the lumen. Slight migration of the stent occurred, with some inflammatory reaction. Two patients with carcinoma were treated in this fashion for dilation of postoperative bronchial stenoses. Although this preliminary report shows some promise for this technique, a disadvantage of this stent is that it cannot be removed after placement. The stent becomes incorporated into the tracheal wall and would require an open procedure for its removal.

Minimal laser energy should be used to remove scar tissue so as to avoid thermal trauma to surrounding tissues. Questions arise as to which laser would be most beneficial for this purpose. There is a definite theoretic preference for the CO_2 laser wavelength over the Nd:YAG laser wavelength. The Nd:YAG laser has a greater coagulation than cutting effect, whereas the CO_2 laser is a more precise cutting device.[11] Despite this theoretic advantage of the CO_2 laser, one of the authors (J.-F.D.) has used the Nd:YAG laser for treatment of patients with tracheal stenosis with great success, by using high power density laser energy with short pulses to minimize surrounding heat-induced tissue damage. The Nd:YAG laser fiber is applied close to the target tissue, within 2 mm, delivering 30 to 40 W with short exposures (0.5- to 0.7-second intervals), which facilitate better cutting with less tissue coagulation.

Mechanical dilation after atraumatic laser incision is an important part of the therapy. We prefer to use rigid bronchoscopes with gradually increasing diameters for maximum dilation. The bronchoscope should be used very gently in a circular motion to dilate gradually the stenotic area. This technique is far less traumatic than the use of rigid bougies.

The largest possible T-tube stent should be placed after the dilation is completed. Size 12 to 14 Montgomery T-tube stents are usually satisfactory. Placement of the stent through the tracheotomy is well described in the literature. It is important, however, to stress that the T-tube should be plugged externally to avoid complications. Plugging the T-tube provides natural humidification to prevent the drying of secretions and also restores the patient's ability to phonate and to carry on daily activities without dyspnea. Meticulous postoperative care of the T-tube is absolutely necessary. Antibiotics, usually amoxicillin or a cephalosporin, are administered after operation for 10 days. Steroids are not administered routinely after operation for fear of delayed epithelialization. A detailed discussion of the management of the Montgomery T-tube has been published.[12] Patients are followed monthly in the outpatient department and are extubated in the operating room under general anesthesia after approximately 6 months. Bronchoscopy is performed at the same time to assess the final result as well as to remove any granulation tissue that may have formed. The patient is observed carefully in the hospital for 24 hours after extubation before discharge.

In conclusion, although complete cervical or subglottic tracheal obstruction can be a challenging management problem, successful endoscopic management is certainly possible. We prefer the technique of atraumatic laser application followed by gentle progressive dilation and stenting with a silicone T-tube left in place for a minimum of 6 months. A high success rate with this technique has justified this approach as an initial therapeutic modality. If persistent stenosis occurs or recurs, open surgical intervention clearly is indicated.

REFERENCES

1. Simpson GT, Strong MS, Healy GB, Shapshay SM, Vaughan CW. Predictive factors of success or failure in the endoscopic management of laryngeal and tracheal stenosis. Ann Otol Rhinol Laryngol 1982;91:384-8.

2. Koufman JA, Thompson JN, Kohut RI. Endoscopic management of subglottic stenosis with the CO2 surgical laser. Otolaryngol Head Neck Surg 1981;89:215-20.

3. Ossoff RH, Tucker GF Jr, Duncavage JA, Toohill RJ. Efficacy of bronchoscopic carbon dioxide laser surgery for benign strictures of the trachea. Laryngoscope 1985;95:1220-3.

4. Dedo HH, Sooy CD. Endoscopic laser repair of posterior glottic, subglottic and tracheal stenosis by division or microtrapdoor flap. Laryngoscope 1984;94:445-50.

5. Montgomery WW. T-tube tracheal stent. Arch Otolaryngol 1965;82:320-1.

6. Shapshay SM, Beamis JF Jr, Hybels RL, Bohigian RK. Endoscopic treatment of subglottic and tracheal stenosis by radial laser incision and dilation. Ann Otol Rhinol Laryngol 1987;96:661-4.

7. Montgomery WW. Current modifications of the salivary bypass tube and tracheal T-tube. Ann Otol Rhinol Laryngol 1986;95:121-5.

8. Westaby S, Jackson JW, Pearson FG. A bifurcated silicone rubber stent for relief of tracheobronchial obstruction. J Thorac Cardiovasc Surg 1982;83:414-7.

9. Duvall AJ, Bauer W. An endoscopically-introducible T-tube for tracheal stenosis. Laryngoscope 1977;87:2031-7.

10. Wallace MJ, Charnsangavej C, Ogawa K, et al. Tracheobronchial tree: expandable metallic stents used in experimental and clinical applications. Work in progress. Radiology 1986;158:309-12.

11. Shapshay SM. Laser applications in the trachea and bronchi: a comparative study of the soft tissue effects using contact and noncontact delivery systems. Laryngoscope 1987;97(suppl 41).

12. Montgomery WW, Montgomery SK. Manual for use of Montgomery® laryngeal, tracheal and esophageal prostheses. Ann Otol Rhinol Laryngol 1986;95(suppl 125).

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INTERNATIONAL CONFERENCE AND WORKSHOP
HEAD AND NECK CANCER REHABILITATION

An International Conference and Workshop on Head and Neck Cancer Rehabilitation will be held March 14-18, 1990, at the Ritz Carlton Hotel in Dearborn, Michigan. For further information, contact Department of Otolaryngology, Wayne State University, School of Medicine, 4201 St Antoine, 5E-UHC, Detroit, MI 48201; (313) 577-0804.

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FRONTAL SINUS OSTEOMA

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Osteoma is the most common benign tumor of the nose and paranasal sinuses, and the frontal sinus is its most frequent location. This tumor may be discovered incidentally on radiographs or may enlarge to produce symptoms and, rarely, complications referable to its location near the orbit and anterior cranial vault. A series of 22 cases of frontal sinus osteoma treated at the UCLA Center for the Health Sciences is reviewed. The presenting symptoms of this tumor, patient examination, radiographic evaluation, diagnosis, and indications for surgical and nonsurgical management are discussed. Various surgical approaches are reviewed, with emphasis on the advantages and disadvantages of each technique. Issues at surgery include the location of the surgical incision, technique of sinus entry, tumor removal, status of the posterior sinus table, patency of the nasofrontal duct, sinus obliteration, and avoidance of cosmetic deformity. Patient outcomes are assessed and recommendations given based on our findings and experience.

KEY WORDS — frontal sinus, osteoma, osteoplastic flap, paranasal sinus neoplasms.

Osteomata of the frontal sinus are uncommon but certainly not rare.[1-4] In 1941, Teed[1] reviewed and summarized 321 cases from the literature up to that time. From the Mayo Clinic, Hallberg and Begley[2] in 1950 reported on 40 cases. In an updated review 29 years later from the same institution, 16 frontal sinus osteomas and 12 in the frontoethmoid region were seen.[3] Furthermore, these and other recent surveys confirm that the frontal sinus is the most common sinus location of these benign neoplasms.[4-6]

The histopathologic nature of paranasal sinus osteoma has been reviewed in an extensive clinicopathologic study by Fu and Perzin.[6] A paranasal sinus osteoma consists of well-defined mature osseous tissue found in the wall of the sinus and filling its cavity. There are two characteristic histologic types. The "ivory" or eburnated osteoma is composed of hard, dense bone that contains only a minimal amount of fibrous tissue. The "mature" osteoma, or osteoma spongiosum, contains mature cancellous bone and may be found at the periphery of ivory osteomas. Occasionally, a third variety called "mixed" osteoma contains features of both ivory and mature osteomas. Osteomas are benign, are generally well localized and discrete, and show little tendency to recur after excision unless incompletely excised.

A differential diagnosis of frontal sinus osteoma can be formed by consideration of other fibro-osseous lesions of the paranasal sinuses. These lesions may have a similar radiographic appearance, but their borders are less well defined than those of osteomas. Fu and Perzin[6] separate osteomas from these less common lesions, which include fibrous osteoma, fibrous dysplasia, and ossifying fibromas. First, fibrous osteoma is basically an osteoma with a greater amount of intertrabecular fibrous tissue than seen in ivory or mature osteomas. It occurs in the same older age group and has the same benign behavior as typical osteomas. Fibrous dysplasia, on the other hand, has several differentiating characteristics. Radiographically, it appears poorly defined and irregular. It tends to appear at a younger age, often in the first or second decades. Histopathologically, fibrous dysplasia is without a capsule and has mildly to highly cellular spindle-shaped fibroblastic cells and irregular trabeculae of woven bone without osteoblastic lining or cement lines. It is believed to be an arrest of normal ossification at the woven bone stage, without progression to lamellar bone. This diffuse benign process has a tendency to recur after incomplete excision. If treated with radiation therapy, malignant transformation to osteogenic sarcoma may occur. A third lesion, ossifying fibroma, also occurs at a young age. Microscopically, it has mainly fibrous and some osseous tissue. A highly cellular fibrous stroma at various degrees of maturity is combined with osseous tissue containing osteoid and osteoblasts. A specialized variant of this entity is the "psammomatoid" ossifying fibroma that occurs typically in young children in the region of the ethmoid sinuses.[7] Clinically, ossifying fibroma tends to have a more aggressive clinical behavior that requires more extensive surgical treatment. Other rare fibro-osseous tumors of the paranasal sinuses include benign osteoblastomas, giant cell tumors, and osteosarcomas.

A rare but important clinical manifestation of sinus osteomas occurs in conjunction with Gardner's syndrome.[8,9] This is an association of osteomas, soft tissue tumors (epidermal and/or sebaceous cysts or subcutaneous fibrous tumors), and polyposis of the bowel. The significance of this syndrome lies in the fact that though the bone and soft tissue tumors are benign, "malignant degeneration" of intestinal polyps occurs in nearly 40% of cases.[10] This syn-

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drome also carries a familial dominant hereditary pattern. The head and neck manifestations of this rare condition, such as osseous tumors of the mandible, skull, and sinuses, are frequently the initial findings. In a recent series one case of Gardner's syndrome presented with a frontal sinus osteoma.[9]

The cause of frontal sinus osteomas is unknown and speculative. Three main theories have been proposed that involve developmental, traumatic, or infectious causes.[3] The developmental theory postulates that osteomas arise at the junction of the embryonic cartilaginous ethmoid and membranous frontal bones. However, many frontal sinus osteomas are located far from the frontoethmoid junction. Traumatic origins of frontal sinus osteomas do not explain the large numbers of patients with this tumor who lack a history of trauma.[3] Infection also plays a role; several series cite a 30% incidence of associated infection with frontal sinus osteomas.[3,11] It is difficult to tell if infection is primarily or secondarily associated in these cases. Whatever their cause, these tumors do occur and have a more predictable growth pattern.

In 1951 Gibson and Walker[12] wrote that "evidence of the rate of growth [of frontal sinus osteomas] is scanty, but most writers consider it slow but inexorable." In a recent report, the growth of a frontal sinus osteoma was followed radiographically for 17 years.[13] In the first 10 years, a small osteoma on the roof of the left frontal sinus enlarged to fill the entire left side almost completely. After 7 more years of asymptomatic growth, the tumor was removed following an episode of acute frontal sinusitis. With the slow growth pattern of these lesions comes a wide range of clinical presentations.

The age of presentation of frontal sinus osteomas is commonly reported to be the second through fifth decades.[3-5,14] Only two cases have been reported in children under 10 years.[4] An older age range of presentation in the fourth, fifth, and sixth decades was reported by Atallah and Jay.[9] In their series of 23 patients, 18 of European origin presented later in life, while four patients from the Middle East and one from the West Indies had symptoms by or before the fourth decade, suggesting ethnic differences in age at presentation. A majority of reports indicate a male to female predominance of about 2:1.[4,9] Two recent surveys have not confirmed this.[3,15] In contrast, another current series from Norway found a male to female ratio of 3.75:1 in 19 cases.[14]

The clinical presentation of frontal sinus osteoma covers a wide spectrum. This probably is related to the slow growth of these tumors. Many are asymptomatic and discovered only with skull radiography.[16] The most common symptom is frontal or facial pain and headache.[9,14] Frontal sinus infection also is seen commonly in association with frontal sinus osteoma.[4,9] The enlarging osteoma can outgrow the confines of the frontal sinus anteriorly, inferiorly, or posteriorly. Anterior extension produces deformity of the forehead contour. With inferior growth, orbital symptoms of proptosis, diplopia, or amaurosis fugax are seen.[1,3,9,17] Posterior intracranial extension may lead to meningitis, seizures, or hemiparesis.[17,18] This wide range of symptoms seen with frontal sinus osteomas, including the asymptomatic or minimally symptomatic presentations of large osteomas in patients recently seen at the UCLA Center for the Health Sciences, prompted us to review our experience with treatment of this interesting tumor.

METHODS

A patient record search was conducted at the UCLA Center for the Health Sciences medical records and pathology departments. From the years 1957 through 1988, 22 cases of frontal sinus osteoma treated surgically at this institution were identified and the charts reviewed. When possible, contact with outside physicians for long-term follow-up was made.

RESULTS

The patient group consisted of 12 men and ten women ranging in age from 18 to 75 years. In our series, the most common presenting symptom of frontal sinus osteoma was frontal headaches in 15 patients (68%), with an average duration of 1.7 years (range, 2 months to 6 years). This was followed by frontal pain in four patients (18%) lasting from 1 month to 5 years. Two patients (9%) were asymptomatic. Twenty-three percent of patients had a history of sinus infections, and one patient (5%) gave a history of prior trauma to the frontal region.

Two patients underwent frontoethmoidectomy and osteoma excision; one patient had the procedure twice, the second time 5 years later for osteoma recurrence. No further osteoma excisions via this approach were done after 1962. Eight patients underwent the osteoplastic flap technique and osteoma excision without sinus obliteration. Thirteen patients underwent frontal sinus obliteration with abdominal fat graft in addition to the osteoplastic flap technique.

Microscopic evaluation of osteomas was done in 16 cases. Three specimens were found to be ivory osteomas; nine, mature osteomas; and four, of the mixed type.

Early postoperative complications were seen in two patients. One patient developed CSF leak and rhinorrhea 2 days postoperatively. While his osteoma had been located on the inferior-medial frontal sinus floor extending into the ethmoid sinus, no dural tear or cribriform plate disruption had been noted during surgery. The patient was treated with lumbar puncture, and his rhinorrhea resolved in 2 days, with no further sequelae. A flap hematoma was seen in one patient who had a coronal skin flap. This required hematoma evacuation and a blood transfusion.

Long-term (>1 year) follow-up of 12 patients was available. Four patients developed recurrent headaches. Two of these patients returned 6 and 8 years following osteoma excision and sinus obliteration with complaints of headaches. They were found to have ethmoid sinusitis and were treated medically with success. One patient who underwent osteoma excision without sinus obliteration returned 19 years later complaining of headaches similar to those experienced before osteoma surgery. A computed tomographic scan showed a small osteoma in the region of prior surgery, with normally aerated frontal sinuses and no mucocele. She currently is being treated for migraine headaches. One patient who underwent two frontoethmoidectomies for frontal sinus osteoma presented 14 years later with frontal headaches. Sinus tomographs were suggestive of a frontal sinus mucocele. The patient, however, refused surgery and was lost to follow-up.

With regard to the role of sinus infections and frontal sinus osteoma, the findings were mixed. Five patients (22%) gave a history of sinus infections. Of these patients, however, in only one was infectious, obstructive sinus mucosal disease found at surgery. On the other hand, in three patients with no history of sinus infections, frontal sinus mucosal disease (polypoid thickening, mucocele, mucopyocele) was discovered.

DISCUSSION

In most cases, the indications for surgery in the treatment of frontal sinus osteomas are well agreed on.[9] The finding of an osteoma in the presence of symptoms is most generally the situation in which surgical intervention is justifiable. The known growth history of osteomas, with potential for orbital or intracranial complications, requires surgery to prevent development of these problems. However, in the case of an asymptomatic osteoma, the indications are not as clear.

Asymptomatic osteomas are frequently encountered. Childrey[16] reviewed 3,510 consecutive skull radiographs taken for any reason and found an incidence of frontal osteomas of 0.43%. Teed[1] advocated removal of any osteoma, regardless of size; however, his position is not uniformly accepted.[3,9] Patients with no symptoms or minimal symptoms may be followed up with serial x-ray studies to assess osteoma growth and changes in symptomatology. This was the treatment of two patients in our series, who were followed up for 6 months and 3½ years, respectively, before surgery. The need for follow-up must be explained to the patient. Though not all osteomas grow sufficiently to produce symptoms, the serious complications of excessive growth of these tumors has been well documented.[1,3,13,18]

The techniques of surgical management of frontal sinus osteomas merit a detailed review. Prior to use of the osteoplastic flap, the standard frontoethmoidectomy approach to the frontal sinus was used.[1] The technique of osteoplastic flap approach to the frontal sinus was described in 1894.[19,20] It went through several modifications[12,21] and, since being popularized by Goodale and Montgomery[22,23] in the 1950s and 1960s, has been a standard approach to diseases of the frontal sinus. In the treatment of frontal sinus osteomas, it has been used exclusively at our institution since 1962. Issues to be considered with this technique in treating frontal sinus osteomas include the location of the skin incision, unilateral versus bilateral sinus entry, the status of the posterior frontal sinus table and nasofrontal duct, and obliteration of the sinus.

The location of the skin incision influences several aspects of surgical management, including operative exposure, surgical blood loss, and postoperative paresthesias and cosmesis. Regarding the location of the skin incision (brow versus coronal), the review of Hardy and Montgomery[24] reported use of the brow incision in three fourths of their patients who underwent the osteoplastic flap technique for all types of frontal sinus disease, including osteomas. Of these, 60% of the brow incisions were unilateral. The brow incision (external frontal approach) also was used predominantly in other recent series of frontal sinus osteoma patients.[4,9] In our series, we treated 21 patients with the osteoplastic flap technique. In seven patients (33%) we used brow incisions (unilateral in three and bilateral in four), and in 14 patients (67%) we used coronal incisions.

Surgical blood loss associated with incision technique was reported also by Hardy and Montgomery.[24] As would be expected, average blood loss was 250 mL for a unilateral brow incision, 350 mL for a bilateral brow incision, and 650 mL for a coronal incision. In our series, average blood loss was 225 mL for a unilateral brow incision, 300 mL for a bilateral brow incision, and 450 mL for a coronal incision. The two patients in our series who received blood transfusions following surgery had coronal flaps. When elective surgical treatment using the coronal incision is anticipated, blood supply via autologous donation or a designated donor may be considered.

The coronal incision in the osteoplastic flap approach to frontal sinus osteomas has been used frequently at our institution on men and women, except men with pattern baldness or a family history of such. In our experience the coronal incision yielded higher patient satisfaction, because the scar was hidden behind the hairline. Patients also complained less of brow and forehead paresthesias when it was used.

In connection with the coronal skin incision, the bilateral frontal sinus osteoplastic flap and sinus entry technique has been used frequently at our institution and in 77% of the patients in our series. Several factors may have played a role in this. First, in review of our series, four patients had bilateral frontal sinus osteomas, all of which included small osteomas on the opposite side that only were appreciated intraoperatively during sinus exposure via a bilateral osteoplastic flap technique. Second, patient satisfaction with forehead profile appearance was higher following a bilateral osteoplastic flap technique than following a unilateral flap technique.

After sinus entry and osteoma exposure, the status of the posterior frontal sinus table and nasofrontal duct is an important consideration. Our series was reviewed to determine osteoma location in relation to the posterior table and nasofrontal duct. In 19 charts, the location of the osteoma was determined by description in the operative report. Seven patients had osteoma arising from the posterior sinus table, and none had wall erosion. In eight patients, the osteoma was felt to obstruct the nasofrontal duct. Next, the significance of the proximity of osteoma to these structures was investigated.

The posterior frontal sinus table was considered first. In our experience, during osteoma removal from the posterior table, exposure of dura occurred in three patients. No dural tears were seen. The sinuses were all obliterated and the patients had no complications. This series had no cases of posterior table erosion by osteoma; however, Hardy and Montgomery[24] reported this in six of 25 of their frontal sinus osteoma patients. Good results also were reported with sinus obliteration. When the osteoma extends into the anterior cranial fossa, a combined craniofacial approach to these tumors has been required.[18,25]

The nasofrontal duct of the frontal sinus lies at the medial-inferior aspect of the sinus floor. In our series we frequently found osteomas at this location. In two of eight patients in whom the osteoma appeared to obstruct the nasofrontal duct, we found concomitant obstructive sinus mucosal disease. Conversely, we found no sinus mucosal disease in six patients with similarly "obstructing" osteomas.

After osteoma removal, the issue of obliteration of the frontal sinus is considered. The technique of obliteration of the frontal sinus with adipose tissue has been reviewed by several authors.[24,26-28] Montgomery has shown in dogs that transplanted fat tissue remains viable and no osteogenesis occurs.[29] This technique has been used successfully in management of all types of frontal sinus disease. In their large series of the osteoplastic flap technique, Hardy and Montgomery[24] reported that 83% of patients had sinus fat obliteration and 17% did not. Of those who had obliteration, 4% required revision surgery. In the group not receiving obliteration, 10% needed revision surgery. The most common reason for revision was recurrent chronic sinus infection. Unfortunately, their report did not detail separately the patients with frontal sinus osteoma, 10% of the 250 patients in their series. They advocated that "adipose obliteration should be accomplished in all cases, regardless of etiology, unless suspected malignant disease is encountered."[24] It was emphasized that frontal sinus disease may recur decades after initial treatment. They speculated that even their 19-year follow-up may have been inadequate in determining the long-term fate of frontal sinuses obliterated with an adipose graft.

Zonis et al[21] reported on 15 frontal sinus osteoma patients treated with the osteoplastic flap technique. They divided their group into those in whom no concomitant sinus mucosal infectious disease was present at surgery and those in whom infection was present. In nine patients in the former group no fat obliteration was performed. In four of six patients in the latter group, including two with large posterior table defects, fat obliteration was accomplished. Zonis et al reported good results in both groups; however, the patients were followed up for 5 years or less.

In our series, sinus obliteration was accomplished by harvest of adipose tissue from the abdomen and removal of all vestiges of sinus mucosa by curettage and drill. The complete removal of sinus mucosa has been strongly emphasized.[30] In Hardy and Montgomery's series,[24] three of eight patients with recurrent chronic frontal sinus infection following the osteoplastic flap technique did not have complete removal of sinus mucosa at the first operation, according to the operative reports. Before placement of adipose tissue in the sinus cavity, a strip of frontal bone pericranium, exposed via the coronal incision, was placed in the sinus floor covering the nasofrontal ducts and over defects of the posterior table.[31] An adipose graft then was placed in the sinus, the bone flap was replaced, and the wound was closed. The pericranial graft provided additional support for the graft at the sinus floor and further plugging of the nasofrontal ducts. Fat graft obliteration of the frontal sinus with use of this technique was performed on the last eight patients in our series.

CONCLUSIONS

Based on review of our experience, the following recommendations are given for a frontal sinus osteoma encountered in clinical practice. The first question to be asked regarding indications for surgery is, "Is the osteoma symptomatic?" In general, the symptomatic osteoma should be removed. For asymptomatic osteomas, the following guidelines are suggested. A CT scan of the sinuses should be performed for delineation of the location and extent of the tumor. If the osteoma is located at the nasofrontal duct or occupies greater than 50% of the volume of the frontal sinus, it should be removed. Small and laterally located osteomas may be watched, provided the patient understands the potential for growth and has close follow-up, with repeat CT scan in 6 months to 1 year and return if symptoms arise.

In the surgical treatment of frontal sinus osteomas, the following suggestions are given. The coronal incision should be used whenever possible, except if a receding hairline or family history of male pattern baldness precludes its use. In this case a bilateral brow incision is used. A bilateral osteoplastic flap technique, with removal of the intersinus septum, is recommended for improved exposure and visualization of tumor extent. After the frontal sinuses are exposed and the tumor is removed, both frontal sinuses are obliterated with a pericranial graft and abdominal fat, regardless of the presence or absence of sinus mucosal disease. In our experience, improved results and increased patient satisfaction have been observed with application of these management principles.

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REFERENCES

1. Teed RW. Primary osteoma of the frontal sinus. Arch Otolaryngol 1941;33:255-92.

2. Hallberg OE, Begley JW Jr. Origin and treatment of osteomas of the paranasal sinuses. Arch Otolaryngol 1950;51: 750-60.

3. Wilkes SR, Trautmann JC, DeSanto LW, Campbell RJ. Osteoma. An unusual cause of amaurosis fugax. Mayo Clin Proc 1979;54:258-60.

4. Samy LL, Mostafa H. Osteoma of the nose and paranasal sinuses with a report of 21 cases. J Laryngol Otol 1971;85:449-69.

5. Gil-Carcedo LM, Alarcos A, Alarcos E, Izquierdo JM. Osteomas. Survey of 26 cases. Part three. Indications and treatment. An Otorrinolaringol Ibero Am 1987;14:367-87.

6. Fu YS, Perzin KH. Non-epithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx: a clinicopathological study. II. Osseous and fibro-osseous lesions, including osteoma, fibrous dysplasia, ossifying fibroma, osteoblastoma, giant cell tumor, and osteosarcoma. Cancer 1974;33:1289-1305.

7. Margo CE, Weiss A, Habal MB. Psammomatoid ossifying fibroma. Arch Ophthalmol 1986;104:1347-51.

8. Batsakis J. Tumors of the head and neck. Clinical and pathological considerations. 2nd ed. Baltimore: Williams & Wilkins, 1979:405-6.

9. Atallah N, Jay MM. Osteomas of the paranasal sinuses. J Laryngol Otol 1981;95:291-304.

10. Shiffman MA. Familial multiple polyposis associated with soft tissue and hard tissue tumors. JAMA 1962;182:514-22.

11. Rawlins AG. Osteoma of the maxillary sinus. Ann Otol Rhinol Laryngol 1938;47:735-53.

12. Gibson T, Walker FM. Large osteoma of the frontal sinus. A method of removal to minimise scarring and prevent deformity. Br J Plast Surg 1951;4:210-7.

13. Spencer MG, Mitchell DB. Growth of a frontal sinus osteoma. J Laryngol Otol 1987;101:726-8.

14. Boysen M. Osteomas of the paranasal sinuses. J Otolaryngol (Can) 1978;7:366-70.

15. Miller NR, Gray J, Snip R. Giant, mushroom-shaped osteoma of the orbit originating from the maxillary sinus. Am J Ophthalmol 1977;83:587-91.

16. Childrey JH. Osteomas of the sinuses, the frontal and sphenoid bone. Arch Otolaryngol 1939;30:63-72.

17. Soboroff BJ, Nykiel F. Surgical treatment of large osteomas of the ethmo-frontal region. Laryngoscope 1966;76:1068-81.

18. Bartlett JR. Intracranial neurological complications of frontal and ethmoid osteomas. Br J Surg 1971;58:607-13.

19. Schonborn. Cited by Willkop A. Ein Beitrag zur Casuistik der Erkrankungen des Sinus Frontalis. Wurzburg: F. Fromme, 1894.

20. Brieger. Arch Ohren Nasen Kehlkopfheilkd 1895;39:213.

21. Zonis RD, Montgomery WW, Goodale RL. Frontal sinus disease: 100 cases treated by osteoplastic operation. Laryngoscope 1966;76:1816-25.

22. Goodale RL, Montgomery WW. Anterior osteoplastic frontal sinus operation. Ann Otol Rhinol Laryngol 1961;70:860-80.

23. Goodale RL, Montgomery WM. Technical advances in osteoplastic frontal sinusectomy. Arch Otolaryngol 1964;79:522-9.

24. Hardy JM, Montgomery WW. Osteoplastic frontal sinusotomy. An analysis of 250 operations. Ann Otol Rhinol Laryngol 1976;85:523-32.

25. Mugliston TAH, Stafford N. A cranio-facial approach to large osteomas of the fronto-ethmoidal region. J Laryngol Otol 1985;99:979-83.

26. Montgomery WW. Surgery of the frontal sinuses. Otolaryngol Clin North Am 1971;4:97-125.

27. Calcaterra TC, Strahan RW. Osteoplastic flap technique for disease of the frontal sinus. Surg Gynecol Obstet 1971;132: 505-10.

28. Sessions RB, Alford BR, Stratton C, Ainsworth JZ, Shill O. Current concepts of frontal sinus surgery: an appraisal of the osteoplastic flap-fat obliteration operation. Laryngoscope 1972;82: 918-30.

29. Montgomery WW. The fate of adipose implants in a bony cavity. Laryngoscope 1964;74:816-27.

30. Schenck NL. Frontal sinus disease: III. Experimental and clinical factors in failure of the frontal osteoplastic operation. Laryngoscope 1975;85:76-92.

31. Calcaterra TC. Osteoplastic frontal sinusotomy: current methodology and results. Trans Pac Coast Oto-Ophthalmol Soc 1983;64:151-4.

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REEVALUATION OF MAXILLARY SINUS SURGERY: EXPERIMENTAL STUDY IN RABBITS

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Functional endoscopic sinus surgery concentrates primarily on the removal of ostiomeatal complex disease. When required, maxillary sinus ostioplasty is performed. However, surgical widening of a sinus ostium is contrary to common precepts. A study therefore was performed to reevaluate the effects of antrostomies and of intrasinus mucosal removal. Widening of the natural ostium, a separate antrostomy at some distance from the ostium, or radical mucosal removal was performed on 30 rabbits. Fifteen sinuses were used as controls. After 6 to 8 weeks the status of the sinus mucosa and mucociliary clearance was studied. The study confirmed that mucociliary clearance continued toward the natural ostium following inferior antrostomy. Following widening of the natural ostium, mucociliary clearance through the ostium redeveloped in 11 of 18 sinuses but was typically imperfect. There were no cases of ostial closure; however, the incidence of infection was significantly higher in all three experimental groups than in the control group.

KEY WORDS — antrostomy, maxillary sinus ostioplasty, mucociliary clearance.

INTRODUCTION

The natural ostium of the maxillary sinus frequently is widened during functional endoscopic sinus surgery when maxillary sinus disease is present and the opening is stenotic.[1,2] Clinical experience demonstrates that these maxillary ostioplasties have a very high patency rate and appear to develop mucociliary clearance. However, the effects of "violating the virginity" of the ostium have been debated in the literature for over 50 years.[3-6]

In the early part of this century, Siebenmann[7] advocated a middle meatal antrostomy because of the ease of the approach, and Kubo[8] recommended the technique because of its long-term patency. In his book on the nasal accessory sinuses, Hajek[9] also said he had been satisfied with the results. Furthermore, Hajek stated that if closure or marked narrowing of the maxillary ostium was present, it was imperative to open it rather than just create dependent drainage, if recurrent disease was to be avoided.

In the early literature, the primary argument against middle meatal antrostomy was the concept of dependent drainage.[9] Subsequently, the organized patterns of mucociliary clearance were identified. However, concern then developed about the possibility of trauma to the ostium causing permanent damage.[10] In part, this concern appears to have been due to a misconception. Proetz[11] wrote that the primary vascular, lymphatic, and neurologic communications with the sinus occurred via the ostium, in one of his early publications. He went on to say, "When one considers the protracted pain and the paresthesias which follow the section of peripheral nerves elsewhere, the fact of the nerves entering by the ostium assumes a serious aspect from a surgical viewpoint."

Hilding[12] subsequently performed a number of experiments on the effects of stripping mucosa from the frontal and maxillary sinuses of animals. He demonstrated that denuding circular areas of mucosa adjacent to the ostium in the frontal sinus of dogs frequently resulted in closure. He also performed a series of experiments in rabbits, creating antral windows at different sites in the sinuses.[13] He reported difficulty identifying mucociliary clearance in the rabbit and attributed this to the anesthesia. Hilding used three animals in each of three operative groups. At reexploration he found that all three animals in which the natural ostium was widened became infected, whereas only two of three animals in which the opening was made in the inferior portion of the sinus became infected. In another group Hilding created an opening high on the medial wall, as far from the natural ostium as possible, and none of the three animals became infected. Largely as a result of this work, the precept of avoiding surgery on the natural ostium became firmly established and inferior meatal antrostomy became accepted as the approach of choice, despite isolated reports of good results with the middle meatal route.[4-6]

This study was performed to reevaluate the effects of widening the maxillary sinus in a larger series of rabbits than the group operated upon by Hilding. In Hilding's experiments the rabbits with middle meatal antrostomy became infected in the early postoperative period, before mucociliary

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From the Department of Otolaryngology–Head and Neck Surgery, The Johns Hopkins Medical Institutions, Baltimore. Supported in part by Amideast Peace Fellowship Program grant PF2192. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of The Johns Hopkins Medical Institutions.

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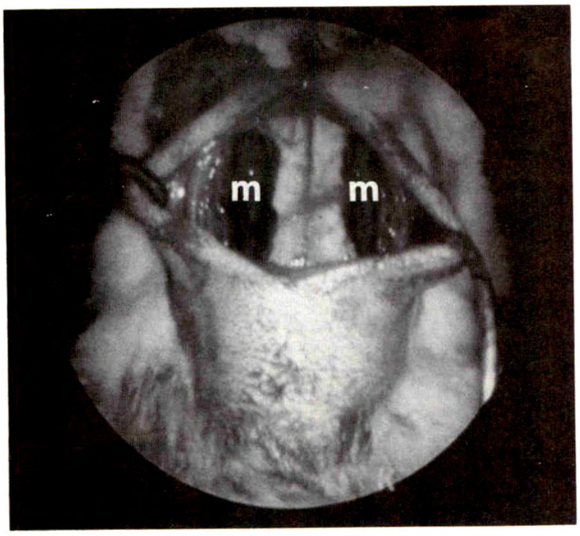

Fig 1. Intraoperative view demonstrating surgical exposure following removal of bone over maxillary sinus (m).

clearance would have become reestablished. In this series, therefore, a decision was made to treat the animals with antibiotics in the early postoperative period, as is frequently performed in the clinical situation. Additionally, the effects of removing all accessible mucosa from the maxillary sinus were evaluated both with and without a separate nasal antral window.

MATERIALS AND METHODS

Thirty New Zealand white rabbits underwent induction of anesthesia with an intramuscular injection of 100 mg of ketamine hydrochloride mixed with 5 mg of acepromazine maleate. This then was supplemented with 6 to 8 mg of intravenous thiamylal sodium prior to the onset of the operation and at 20- to 30-minute intervals during the procedure. The area of the nasal dorsum was shaved, prepared, and draped. A longitudinal midline incision was made over the dorsum of the nose through the skin, subcutaneous tissue, and periosteum. The periosteum was elevated laterally on both sides of the nose. Initial entry into the maxillary sinus was performed with a curette, and the opening then was widened with a small punch (Fig 1). When mucociliary clearance was to be observed at this first procedure, a plastic adhesive drape then was applied and a small perforation created for endoscopic visualization. The maxillary sinus mucosa was irrigated with saline as necessary, to prevent drying. A few drops of india ink were used to allow observation of mucociliary clearance.

The animals were divided into groups for the different procedures. Experimental controls were created by only exposing the maxillary sinus on one side in 15 animals. The type of procedure performed on the remaining sinuses in each group was predetermined and consistent. Three animals died of the initial anesthesia and were replaced.

In 18 sinuses the natural ostium of the sinus was widened anteriorly and inferiorly. In the first seven animals in this group, attempts to widen the natural ostium resulted in some stripping of the adjacent mucosa; in the subsequent 11 animals a less traumatic technique utilizing sharp dissection was performed. In 12 sinuses separate windows were created inferior and anterior to the natural ostium. In four sinuses in this group a strip of mucosa also was removed from the area of the natural ostium.

In 13 sinuses the mucosa was removed as it would be in a radical antrostomy. The precise technique in this group was varied slightly as it might be in Caldwell-Luc procedures. In five sinuses within this group a nasal antral window also was created, and in four, care was taken to leave the mucosa of the ostial area intact. Two of the original 60 sinuses were excluded from the study because of technical problems during the operative procedure.

The incision on the dorsum of the nose of each animal was closed in two layers with running 4-0 polyglactin 910 sutures. The animals received 300,000 units penicillin G, benzathine and penicillin G procaine suspension intramuscularly every other day for 2 weeks. At each injection, the animals were examined for evidence of erythema or swelling of the nasal dorsum or for nasal discharge.

The animals were reexplored 6 to 8 weeks after the initial operation. Similar anesthesia and operative techniques were used. The presence or absence of discharge or soft tissue within the sinus was noted, and the appearance of the mucosa observed under magnification. The sinus was considered infected when there was evidence of discharge or mucosal thickening within the sinus. A few drops of india ink then were applied to the floor of the sinus, and a plastic drape was applied and perforated to allow access with a 4-mm telescope. The presence or absence of mucociliary clearance was observed and documented with serial photographs. In some sinuses videotaping of the mucociliary transport also was performed. Any abnormalities of the mucociliary transport pattern were observed and documented. If, over time, mucociliary transport ceased, the sinus was irrigated with normal saline and the transport reexamined. When mucociliary transport had been documented completely, the animals were killed painlessly with an overdose of sodium pentobarbital.

RESULTS

Initial Procedure. At the initial operative procedure, nine sinuses (15%) in six animals appeared infected. The type of operation performed on these sinuses was not changed because of the presence of infection (five in the nasal antral window group, two in the ostioplasty group, and two in the radical antrostomy group), and four of the sinuses were clear of infection at reexploration.

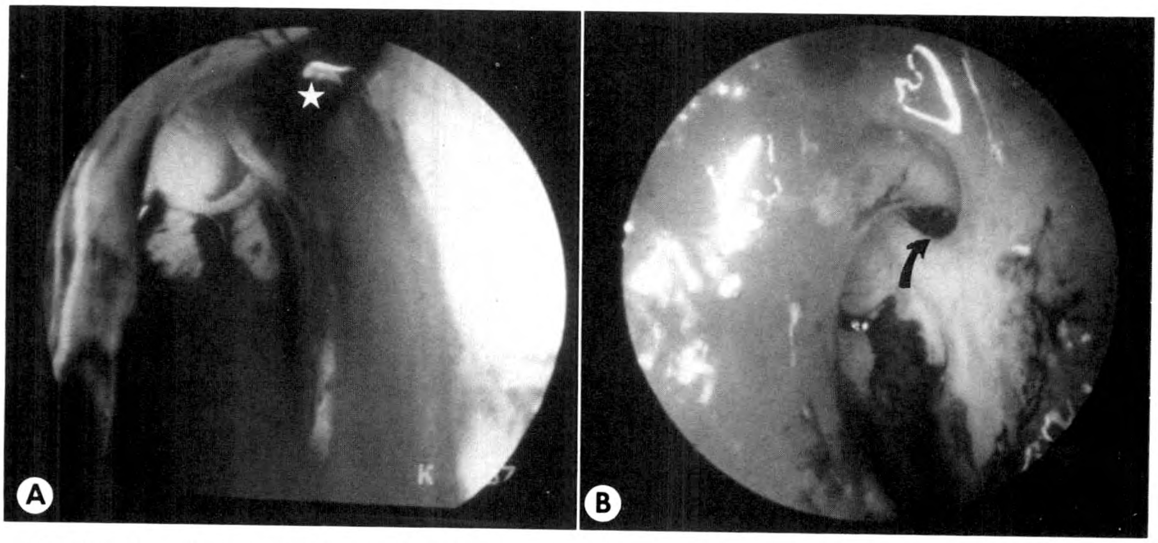

Fig 2. Endoscopic views of right maxillary sinuses used as surgical controls. India ink had been instilled and is seen passing toward ostium. A) Unusually brisk mucociliary clearance passing superiorly toward ostium (star) and out into nose. B) More typical clearance pattern toward natural ostium (arrow).

The pattern of mucociliary clearance was noted to be similar to that previously reported in humans, spreading out in a star-shaped pattern from the floor, up the walls, and toward the natural ostium. The ink typically moved at a speed of 10 to 15 mm/min, with the speed increasing as the ostium was approached. Mucociliary clearance was markedly slowed or stopped by the effects of airflow and drying.

Control Group. In the control group (n = 15), all sinuses healed well, but three (20%) had evidence of infection. In one sinus the natural ostium appeared to be closed as a result of accidental trauma at the first procedure. Mucociliary clearance was present in 13 (87%) with pattern unchanged from the initial procedure (Fig 2).

Nasal Antral Window. All the sinuses in this group (n = 12) healed well, and 11 (92%) of the antrostomies remained patent. Infection was present in five sinuses (41%), and mucociliary clearance in ten (83%). There was no redirection of the mucociliary clearance pattern. Mucociliary clearance remained toward the natural ostium, and no difference was observed in those sinuses in which a strip of mucosa was removed from the area of the ostium. Some mucociliary clearance did take place through the inferior aspect of the antrostomy and into the nose when that opening lay in the path of the mucociliary clearance tracks. In six sinuses (50%) mucociliary clearance also was noted as being into the sinus along the superior edge of the antrostomy. In each of these six sinuses the ink was seen to leave the sinus through the natural ostium and reenter through the antrostomy. It then recirculated out through the natural ostium (Fig 3).

Ostioplasty Group. In the ostioplasty group (n = 18), all the widened ostia remained patent, but infection was present in 11 (61%) of the sinuses. In three sinuses an abscess formed over the bridge of the nose in the early postoperative period. One of

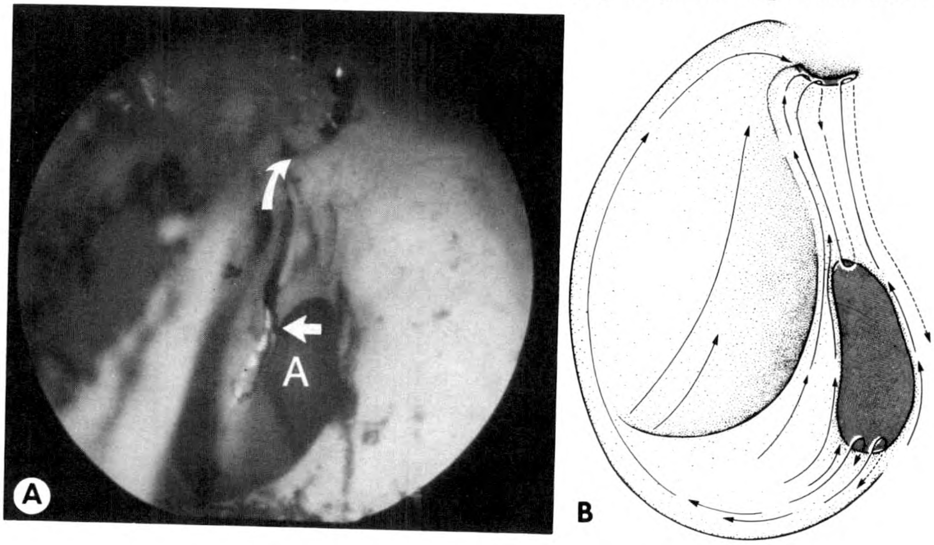

Fig 3. Right maxillary antrum following secondary antrostomy. A) Endoscopic view demonstrates recirculation of ink into sinus (straight arrow) through superior edge of antrostomy. It exits again through natural ostium (curved arrow). B) Artist's representation of mucociliary clearance seen in A. There is some mucociliary clearance into nose through inferior edge of antrostomy. Recirculation of mucus into sinus is present at superior aspect of antrostomy.

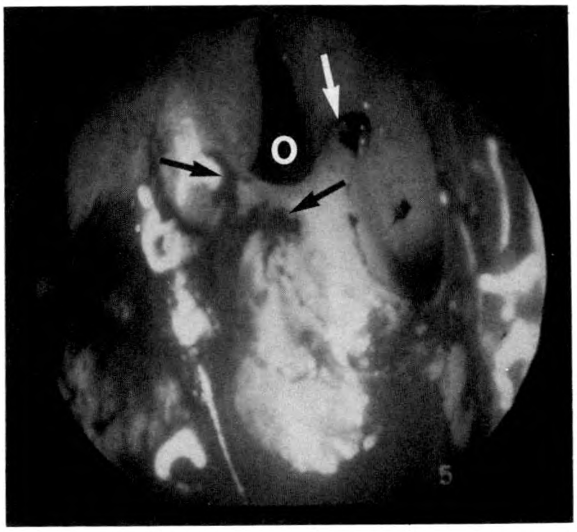

Fig 4. Endoscopic view of left maxillary sinus following widening of natural ostium (O). Ink is seen passing toward inferior aspect of opening (black arrows). More posteriorly, ink is seen passing out of ostium (white arrow).

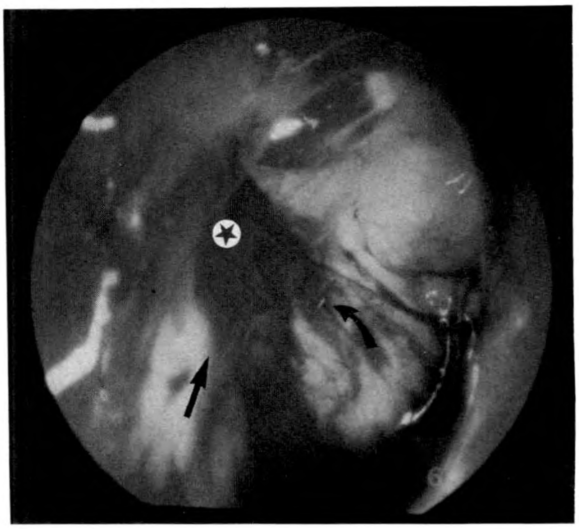

Fig 5. Endoscopic view of cyst in left maxillary sinus following radical removal of mucosa. Cyst does not communicate with ostium, but there is mucociliary clearance (arrows) up medial wall of cyst to point at which ink collects (star). From this point, ink falls by gravity to floor of sinus.

these abscesses resolved, and the remaining two were found to have become isolated from the sinus at the time of reexploration. Mucociliary clearance was present in 13 (72%) of the sinuses, and the dye was seen to pass through the ostium in 11 (61%). In general, however, mucociliary clearance was weaker than in the control group, and imperfect in the ostial area. The normal speed gradient present within the sinus was absent, and the dye tended to collect inferiorly in the area in which the ostium had been extended (Fig 4).

Radical Antrostomy Procedures. In this group (n = 13), the sinus cavity was typically very retracted in size. There was evidence of new bone growth and considerable fibrous tissue. In some sinuses the medial wall was retracted laterally into the sinus cavity and appeared osteitic. In six sinuses (46%) there were separate cysts that did not communicate with the ostium. The ostium was open in one sinus (8%), stenosed in seven (54%), and closed in five (38%). There was evidence of mucosal infection in eight (62%). Mucociliary clearance was observed in six sinuses (46%) within this group, but the ink was observed to exit through the natural ostium in only two (15%). Mucociliary clearance was also present in some of the cysts. Close observation demonstrated that the direction of mucociliary clearance in these cysts still tended to be toward the natural ostium, although there was no communication with it. In two cysts the ink was seen to collect at a certain point on the medial wall, as if collecting in the area in which an ostium should be, and then fall back to the floor (Fig 5).

DISCUSSION

In the first procedures of this series it was difficult to demonstrate mucociliary clearance. Hilding[13] reported a similar problem and attributed it to general anesthesia with barbiturates. However, the problem appears to be primarily due to drying of the mucosa from the open sinus. With saline irrigation of the sinus and the application of an adhesive plastic drape, mucociliary activity quickly redeveloped, unless the mucosa had become too severely dried. With intermittent irrigation and a tight seal around the observing endoscope, it was then possible to observe mucociliary clearance for several hours. It is clear that the primary mucociliary flow pattern is not from anterior to posterior, as suggested by Hilding,[13] but that it originates from the floor. As in the maxillary sinus of humans, mucociliary clearance was seen to spread out in a star-shaped pattern from the floor and then pass up the walls to the ostium.

There are significant differences between the maxillary sinuses of a rabbit and those of humans. The spontaneous infection rate of the rabbit sinuses in this series was high (15%). It is possible that the infection rate would have been significantly lower if *Pasteurella*-free animals had been used. There are also important anatomic differences that make the extrapolation of the rabbit sinus findings to our patients questionable. In the rabbit the natural ostium of the maxillary sinus is posterior, proximal to the primary areas of nasal resistance. As soon as the sinus is opened the animal begins to exchange air through the sinus, as the route of least resistance. In the early postoperative period the periosteum and skin over the sinus tend to flap up and down with respiration. This marked pressure change and skin movement may account for the abscesses that formed in the early postoperative period over the dorsum of the nose of three animals in which the ostium was widened. A similar phenomenon was

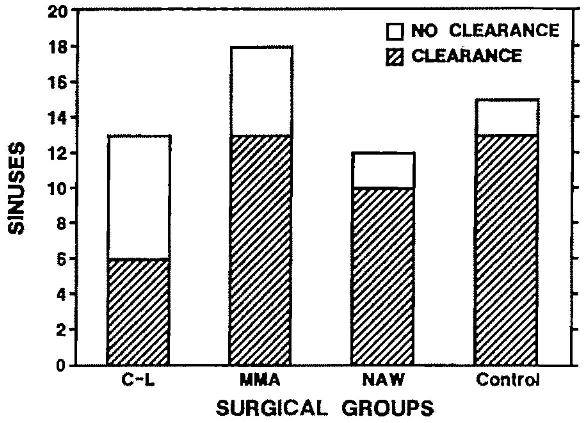

Fig 6. Frequency with which mucociliary clearance was present in different operative groups. In some situations mucociliary clearance was present, but passage of ink through ostium was not documented. C-L — Caldwell-Luc procedure, MMA — middle meatal antrostomy, NAW — nasal antral window.

noted in Hilding's original series, in which all three of his rabbits undergoing widening of the ostium developed a dorsal nasal abscess in the postoperative period.[13] Equalization of these pressure changes also might explain why the least infection was seen by Hilding in the three rabbits in which an antrostomy was created as far anterior in the sinus as possible.

Despite the differences in anatomy, some observations from this study appear to reinforce previous clinical observations. The ostium of the maxillary sinus did not close in any of the 18 sinuses in which it was widened operatively. Clinically, it is also clear that the ostium does not scar closed, but rather has excellent patency over time.[3-5,14] In none of the rabbit sinuses was there any change in direction of mucociliary clearance patterns when a separate antrostomy was performed, or even when the mucosa was stripped out as in a Caldwell-Luc procedure. If mucociliary clearance was present at the second procedure, it always had an orientation similar to that previously present (Fig 6). This also appeared to be true in the limited number of cysts that formed isolated from the ostium following the Caldwell-Luc procedures. In patients, King[15] originally demonstrated in 1935 that mucociliary clearance continued toward the natural ostium after inferior meatal antrostomy. A more recent endoscopic study also has confirmed this observation.[16] However, in this study there was also some mucociliary clearance into the nose through the inferior aspect of the antrostomy when that opening lay in the path of the normal mucociliary clearance pattern.

In 50% of the secondary antrostomy (nasal antral window) sinuses there was some recirculation of mucus back into the sinus through the superior aspect of the opening. A similar phenomenon also has been noted in patients when a middle meatal antrostomy does not connect with the natural ostium.[17] In patients this recirculation appears to be a cause of failure of resolution of maxillary sinus disease following middle meatal antrostomy. However, endoscopic observation of patients also suggests that such recirculation is rare after inferior meatal antrostomy, although it does occur occasionally when the antrostomy is very large.

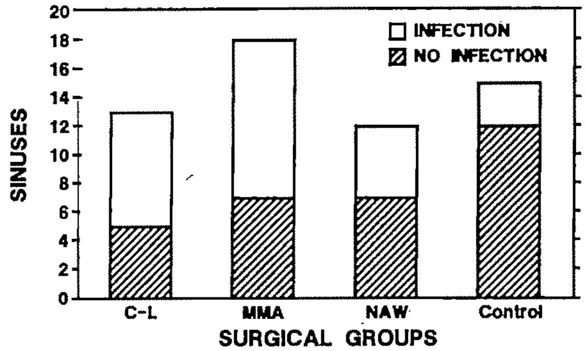

Fig 7 Incidence of infection seen in different operative groups. Presence of mucosal thickening or mucopurulent discharge within sinus was taken as evidence of infection. Infection was greater in treatment groups (Fisher's exact test, p = .03285 [one-tailed]). No statistical difference between treatment groups. Abbreviations as in Fig 6.

Mucociliary clearance has been observed through widened maxillary sinus ostia in patients, although it has not been demonstrated in prior experimental studies. In this study mucociliary clearance was observed occurring through the widened natural ostium into the nose in 61% of the sinuses. However, the mucociliary patterns in the area of the ostium were considerably disturbed, with areas of ink retention Additionally, there was considerable reduction in the overall rate of mucociliary clearance. Although the clinical effects of such a reduction are uncertain, this observation would appear to argue against routine widening of the natural ostium of the maxillary sinus during ethmoidectomy. Rather, it would appear that ostioplasty could interfere with maxillary sinus function if performed in the absence of periosteal disease and that the procedure therefore should be reserved for cases of stenosis or closure. The technique used in the rabbits was, however, considerably cruder than that used in patients. In the latter an attempt usually is made to fold the maxillary sinus mucosa over the inferior edge of the widened opening — a maneuver that was not possible in this series.

At reexploration 61% of the ostioplasty, 41% of the nasal antral window, and 20% of the control procedures had evidence of infection. The difference in infection rate between these two experimental groups and the control sinuses was statistically significant (Fisher's exact test, p = .03285 [one-tailed]), but there was not a statistically significant difference between the two experimental groups. In considering these results, it is important to remember that the experimental sinuses had normally functioning ostia preoperatively, and that different results might have been obtained in the presence of ostial obstruction (Fig 7). There was a correlation between the absence of mucociliary clearance and the presence of infection in the control and two antrostomy groups (Fisher's exact test, p = .0208 [one-tailed]).

The animals in which a radical removal of maxillary sinus mucosa was performed all demonstrated contracted sinuses with fibrous tissue and new bone formation. The medial wall frequently was retracted laterally and appeared osteitic. These are changes that also are observed in some patients after Caldwell-Luc procedures. Interestingly, four of the five sinuses in which antrostomies were performed demonstrated closure of the window. Although the numbers are too small to draw any definite conclusions, this was much higher than the closure in the sinuses in which the mucosa was not removed (one of 12). Mucociliary clearance out of the ostium was generally poor in the radical antrostomy group (15%), and the ostium frequently became stenosed or closed (92%). In a significant number of sinuses in this group (46%), separate cysts had formed that did not communicate with the natural ostium. These findings suggest that this is an operation with a significant chance of causing permanent damage to the sinus.

CONCLUSIONS

Mucociliary clearance patterns in the rabbit maxillary sinus are similar to those seen in humans. There was no tendency for mucociliary clearance patterns to become reoriented following either a separate antrostomy or radical removal of the mucosa. In this study, whenever mucociliary clearance was present it was toward the natural ostium. Widening of the natural ostium did not lead to stenosis, but did lead to some disruption of the normal mucociliary clearance patterns. It therefore would appear preferable not to perform widening of the ostium in patients unless the ostium is closed or stenotic. In the rabbit maxillary sinus, a radical Caldwell-Luc type of procedure typically results in a contracted and scarred sinus with stenosis or closure of the ostium. The formation of separate cysts following this operation was common. These findings add further credence to the concept of performing a conservative sinus procedure rather than a radical mucosal removal as a first procedure.

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REFERENCES

1. Kennedy DW, Zinreich SJ, Rosenbaum A, Johns ME. Functional endoscopic sinus surgery: theory and diagnosis. Arch Otolaryngol 1985;111:576-82.

2. Stammberger H. Endoscopic endonasal surgery — concepts in treatment of recurring rhinosinusitis. Part II. Surgical technique. Otolaryngol Head Neck Surg 1986;94:147-56.

3. Kennedy DW, Zinreich SJ, Shaalan H, Kuhn F, Naclerio R, Loch E. Endoscopic middle meatal antrostomy: theory, technique, and patency. Laryngoscope 1987;97(suppl 43).

4. Wilkerson WW. Antral window in the middle meatus. Arch Otolaryngol 1949;49:463-89.

5. Lavelle RJ, Spencer Harrison M. Infection of the maxillary sinus: the case for middle meatal antrostomy. Laryngoscope 1971;81:90-106.

6. Alusi HA. A new approach to the surgical treatment of chronic maxillary sinusitis. J Laryngol Otol 1980;94:1145-9.

7. Siebenmann E. Beitr Z. Lehre von d. Entstehung und Heilung Rombinierter Nebenhohleneiterungen der Nase. Monatsschr Ohrenheilkd 1912;46:656.

8. Kubo I. Supraturbinale Eroffnung bei der Sinusitis Maxillaris Chronica. Arch Laryngol Rhinol 1912;26:351-6.

9. Hajek M. Pathology and treatment of the inflammatory diseases of the nasal accessory sinuses. St Louis: CV Mosby, 1926.

10. Proetz AW. Essays on the applied physiology of the nose. St Louis: Annals Publishing Co, 1941:356.

11. Proetz AW. The displacement method of sinus diagnosis and treatment. St Louis: Annals Publishing Co, 1931:47.

12. Hilding A. Experimental surgery of the nose and sinuses. II. Gross results following the removal of the intersinus septum and of strips of mucous membrane from the frontal sinus of the dog. Arch Otolaryngol 1933;17:321-7.

13. Hilding AC. Experimental sinus surgery: effects of operative windows on normal sinuses. Ann Otol Rhinol Laryngol 1941;50:379-92.

14. Straatman N, Buiter CT. Endoscopic surgery of the nasal fontanel. Arch Otolaryngol 1981;107:290-3.

15. King E. A clinical study of the functioning of the maxillary sinus mucosa. Ann Otol Rhinol Laryngol 1935;44:480-2.

16. Friedrich JP. Traitement par meatotomies endoscopiques des sinusites maxillaires chroniques. Med Hyg 1984;41:3410-6.

17. Kennedy DW, Zinreich SJ. The functional endoscopic approach to inflammatory sinus disease: current perspectives and technique modifications. Am J Rhinol 1988;2:89-96.

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NEWER TECHNIQUE OF LARYNGEAL REINNERVATION: SUPERIOR LARYNGEAL NERVE (MOTOR BRANCH) AS A DRIVER OF THE POSTERIOR CRICOARYTENOID MUSCLE

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This report analyzes the experience gained using two different techniques to reinnervate the paralyzed vocal cord. In the neurotization group, the superior laryngeal nerve (SLN) motor branch–cricothyroid muscle pedicle was used to reinnervate the posterior cricoarytenoid muscle. In the direct nerve anastomosis group, the SLN was anastomosed to the abductor branch of the recurrent laryngeal nerve (RLN), and the ansa hypoglossi (AH) to the adductor branch of the RLN. A third group of animals (control) had the right RLN sectioned without any anastomosis. About 5 to 6 months postoperatively the animals were killed painlessly and evaluated. The neurotization group revealed vocal fold mobilization on the right side to have an average of about half of the mobility of the left, normal side. After the RLN and SLN on the left were severed as well as the AH bilaterally, the vocal cord mobility was reduced to about one fourth. The direct nerve anastomosis group showed about fourfold less vocal cord mobility than the neurotization group. After the SLN, RLN, and AH were severed bilaterally, the control group showed no vocal cord mobility. The neurotization technique has been selected for further experimentation in human adults.

KEY WORDS — laryngeal reinnervation, posterior cricoarytenoid muscle, superior laryngeal nerve.

A great amount of experimental and clinical scientific work has been done in the field of laryngeal reinnervation, but so far there is no technique that has wide clinical application. We propose to use the superior laryngeal nerve (SLN) motor branch as a driver to the posterior cricoarytenoid (PCA) muscle in order to achieve remobilization of the vocal fold in paralyzed larynges. This report is a follow-up on our recently published article.[1]

MATERIALS AND METHODS

This study compares the experience obtained in two experimental animal models and a control group. The animal used was the dog (beagle). Neurotization (eight dogs) consisted of reinnervation of the right vocal cord with the SLN–cricothyroid (CT) muscle pedicle anastomosed to the PCA muscle. Direct nerve anastomosis (four dogs) consisted of anastomosis of the SLN to the abductor branch of the right recurrent laryngeal nerve (RLN), and the ansa hypoglossi (AH) to the adductor branch of the right RLN. In a control group (four dogs), the right RLN was severed and resected only, without any attempt to reinnervate the PCA muscle. The animals were evaluated 5 to 6 months postoperatively. Electromyographic, histologic, and histochemical studies were performed to evaluate the remobilization of the paralyzed vocal cords. Details of methods used are discussed in our previous publication.[1]

RESULTS

The results of the experimental (neurotization and nerve-to-nerve anastomosis) group and the control group of animals are summarized in Tables 1 and 2. The vocal cord mobility of the left normal side of each dog was graded 10. The mobility of the vocal cord on the right side was compared with the left prior to and after severance of the left RLN, left SLN, and left AH. Four observers graded the vocal cord mobility by watching videotapes. An average was obtained. The mean differential between the two phases of the evaluation (prior to and after severance of the left RLN, SLN, and AH) of the neurotization group was $5.25-2.62=2.63$ ($p<.001$, paired t test; $p=.0039$, Sign test).

The rank sum sample test comparing the neurotization and control groups prior to and after severance of the left RLN, SLN, and AH revealed a p value of .004, which is significant. The mean differential between the two phases of the evaluation of the control group was $1.5-0=1.5$ ($p=.0625$, nonsignificant).

The mean differential between the two experimental groups (neurotization and nerve-to-nerve anastomosis) prior to and after severance of the left RLN, SLN, and AH was statistically significant ($p=.004$ and $p=.0141$, rank sum sample test).

It appears evident that the vocal fold remobilization of the neurotization group is at least fourfold

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From the Departments of Otolaryngology–Head and Neck Surgery (Maniglia, Dodds, Rosenbaum), Pathology (Sorensen), and Neurology (Katirji), Case Western Reserve University School of Medicine and University Hospitals of Cleveland. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Case Western Reserve University.

Presented at the meeting of the American Laryngological Association, San Francisco, April 1-2, 1989.

REPRINTS — Anthony J. Maniglia, MD, 2074 Abington Rd, Cleveland, OH 44106.

TABLE 1. RESULTS OF NEUROTIZATION PROCEDURE

	Right Vocal Cord Mobility (Grade)	
Dog	*Before Severance*	*5 to 6 Months After Severance*
Experimental		
E1	7	4
E2	6	3
E3	7	3
E4	8	5
E5	6	3
E6	3	1
E7	3	1
E8	2	1
	Mean = 5.25	Mean = 2.62
Control		
C1	2	0
C2	1	0
C3	1	0
C4	2	0
	Mean = 1.5	

Normal (left) vocal cord mobility graded 10. "Severance" was of left recurrent laryngeal nerve, superior laryngeal nerve, and ansa hypoglossi. Right superior laryngeal nerve–cricothyroid muscle pedicle had been used to reinnervate posterior cricoarytenoid muscle after severance of right recurrent laryngeal nerve.

greater than that of the nerve-to-nerve anastomosis and control groups.

On electromyography (EMG), dogs E1, E2, E3, E4, E5, and E6 revealed reinnervation potentials as well as fibrillations. Dogs E7, E8, and E11 were not evaluated by EMG because of technical reasons (equipment malfunction). Dog E12 showed reinnervation potential even after the left RLN, SLN, and AH had been transected, in spite of no vocal cord remobilization. Electromyography is not really helpful for evaluation and correlation with vocal cord mobility. Histologic studies using hematoxylin and eosin, Bodian silver stain, and ATPase showing various degrees of regeneration bear no direct correlation with the degree of vocal cord mobilization.[1]

The neurotization technique reported here appears to have sound anatomic and neurophysiologic principles. Although vocal cord mobility in the right side of the experimental neurotization group is limited to about one fourth if compared with the normal side, still there is remobilization of the right vocal cord that might be significant in improving the airway in humans. If the technique could be used clinically, it would eliminate the need for a tracheostomy or arytenoidectomy. Our experiments showed that the direct nerve anastomosis group revealed extremely poor remobilization of the right vocal fold. On the basis of our results, this technique should not be tried in humans.

Our experimental results indicate that laryngeal reinnervation (neurotization technique) using the SLN motor branch–CT nerve-muscle pedicle as a driver to the PCA muscle may represent a successful new surgical approach for remobilization of the vocal fold.

TABLE 2. RESULTS OF DIRECT NERVE ANASTOMOSIS PROCEDURE

	Right Vocal Cord Mobility (Grade)	
Dog	*Before Severance*	*5 to 6 Months After Severance*
Experimental		
E9	2	0
E10	3	1
E11	3	1
E12	2	0
	Mean = 2.5	Mean = 0.5
Control		
C1	2	0
C2	1	0
C3	1	0
C4	2	0
	Mean = 1.5	

Normal (left) vocal cord mobility graded 10. "Severance" was of left recurrent laryngeal nerve, superior laryngeal nerve, and ansa hypoglossi. Right superior laryngeal nerve had been anastomosed to abductor branch of right recurrent laryngeal nerve, and ansa hypoglossi to adductor branch of right recurrent laryngeal nerve.

DISCUSSION

We feel justified in trying the neurotization technique in humans. One of the prerequisites for remobilization of a paralyzed vocal fold is that the arytenoid must show passive mobility. Fixation of the arytenoid by different pathologic processes excludes a patient from eligibility for this proposed procedure.

Two groups of patients who may be eligible are those who have developed bilateral vocal cord paralysis either secondary to trauma such as thyroidectomy or secondary to idiopathic causes. The duration of the vocal cord paralysis should be at least 6 months.

We feel that the neurotization technique, if successful, might provide a better airway as well as a better quality of voice if compared with the classic arytenoidectomy technique. Even if it fails, the patient will still be eligible for the classic arytenoidectomy technique.

Approval for a clinical trial in adults only has been granted by the Institutional Review Board of University Hospitals of Cleveland. We have proposed to try this neurotization technique in eight patients. The sensory branch of the SLN will be preserved. Denervation of the CT muscle after the SLN-CT nerve-muscle pedicle is developed allows for lateralization of the vocal cord, thereby improving the airway. If the animal experimental results can be extrapolated to the clinical trial group, a satisfactory airway, although limited, may very well be adequate to allow permanent decannulation of these patients.

A postoperative period of at least 3 to 6 months would be necessary to evaluate the surgical results. The patient's opposite vocal cord would be the control side in order to compare mobility of the newly reinnervated vocal cord. If this newly proposed surgical procedure is successful, the quality of life of many patients may be improved.

REFERENCE

1. Maniglia AJ, Dodds B, Kumar N, Sorensen K, Katirji MB. Newer techniques of laryngeal reinnervation. Ann Otol Rhinol Laryngol 1989;98:8-14.

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PAN AMERICAN ASSOCIATION OF OTORHINOLARYNGOLOGY–HEAD AND NECK SURGERY

The XXII Congress of the Pan American Association of Otorhinolaryngology–Head and Neck Surgery will be held November 23-27, 1990, in Catagena, Colombia. For further information, contact Pedro Blanco, President, Pan American Congress, Hospital Universitario del Valle, 3er Piso Servicio de Otorrinolaringologia, Cali, Colombia.

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The Casselberry Award was established to encourage the advancement of the art and science of laryngology and rhinology. The award is given for outstanding theses or accomplishments in laryngology and rhinology and consists of a suitable sum of money and a certificate from the Association. Competition for this award is limited to those persons whose abstracts are selected for consideration for inclusion in the annual scientific program. Abstract forms may be obtained from the Secretary, H. Bryan Neel, MD, 200 First Street SW, Rochester, MN 55905. Individuals wishing to compete for this award must submit an entry in the form of a complete thesis to Eugene N. Myers, MD, President, 230 Lothrop Street, Pittsburgh, PA 15213, no later than December 1, 1989. The candidates and theses will be reviewed by a committee. If a winner is selected, the Casselberry Award will be presented at the 111th annual scientific meeting, to be held at the Breakers Hotel in Palm Beach, Florida, April 28-29, 1990.

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FERRET MODEL FOR ACQUIRED SUBGLOTTIC STENOSIS

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Researchers continue to look for an improved animal model for the study of acquired subglottic stenosis. This report describes a ferret model that reliably produces 40% to 60% stenosis with a method analogous to the pathophysiology of prolonged endotracheal intubation. Unlike some previously developed animal models, this model has a low morbidity and a perioperative mortality of less than 5%. Ferrets are small, hardy animals that are inexpensive and easy to house, handle, and anesthetize. They are readily available from breeders in a uniform size, age, and sex. Their airway is disproportionately large for their body size, making them particularly well suited for the study of acquired subglottic stenosis and subsequent surgical therapy.

KEY WORDS — ferret model, subglottic stenosis.

INTRODUCTION

Acquired subglottic stenosis in children most commonly occurs as a result of prolonged endotracheal intubation in a neonate born with infant respiratory distress syndrome. While subglottic stenosis is considered by most investigators to be an infrequent complication of long-term intubation (1.5% to 8.3%),[1-3] there is concern that its incidence is rising because of the increased survival of premature and critically ill newborn infants.[3-5]

The treatment of acquired subglottic stenosis presents a formidable therapeutic challenge. Although an immature soft tissue stenosis due to intubation injury is potentially reversible by medical and endoscopic means, a long-standing stenosis consisting of mature fibrous tissue usually requires some form of operative treatment. In the past, most children were treated by the use of tracheotomy to establish an adequate airway. The perioperative morbidity and mortality of infant tracheotomy, although improved in recent years, is still significant, with some investigators reporting an operative mortality as high as 8.7%[5] and an incidence of delayed complications as high as 30% to 49%.[4,5]

A myriad of techniques have evolved in an attempt to avoid infant tracheotomy. They include endoscopic correction,[6] laser ablation,[7] long-term stenting,[8,9] cricotracheal resection with primary anastomosis,[10] and various combinations of anterior and posterior cricoid splits with and without insertion of autologous grafts.[11-17] There is currently no single operation for the correction of acquired subglottic stenosis.

A paucity of information currently exists comparing the reconstructive options for subglottic stenosis in a prospective fashion. One obstacle to such research is the establishment of a reliable and reproducible animal model. Most prospective animal studies have used the canine model. Although Supance et al[18] have developed a technique that reliably creates 40% to 50% subglottic stenosis following prolonged intubation in mongrel puppies, their model carries with it a 25% perioperative mortality. Furthermore, laryngotracheal reconstructive surgery often necessitates a tracheotomy, which is poorly tolerated in the canine model. Healy[6] has reported a high rate of mortality secondary to tracheal mucous plugs in dogs undergoing tubeless tracheotomy despite daily suctioning and humidification in isolated cages. Moreover, dogs are quite expensive to obtain and house in the laboratory; hence, prospective studies using large numbers are impractical.

Recently a ferret model for the study of postintubation croup was reported by Woods et al.[19] They created a reversible subglottic stenosis by intubating the larynx with a fiberglass test tube brush, and an irreversible subglottic lesion by performing a laryngofissure and stripping the cricoid mucosa. Ferrets are small, hardy animals that are inexpensive to procure and house in the laboratory. In addition, ferrets have a disproportionately large airway for their body size,[20] which would seem to make them an ideal animal model for the study of acquired subglottic stenosis.

The purpose of this study was to attempt to establish a ferret model for acquired subglottic stenosis by inducing stenosis via prolonged endotracheal intubation, thus mimicking the actual pathophysiology that occurs in humans.

From the Department of Otolaryngology, Columbus Children's Hospital and The Ohio State University, Columbus. Supported by the Children's Hospital Research Foundation, grant 75-071, Columbus Children's Hospital, and The Ohio State University Comprehensive Cancer Center Head and Neck Oncology Program, National Institutes of Health/National Cancer Institute grant P30-CA16058. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Children's Hospital Research Foundation, Columbus, Ohio.

Presented at the meeting of the American Laryngological Association, San Francisco, April 1-2, 1989.

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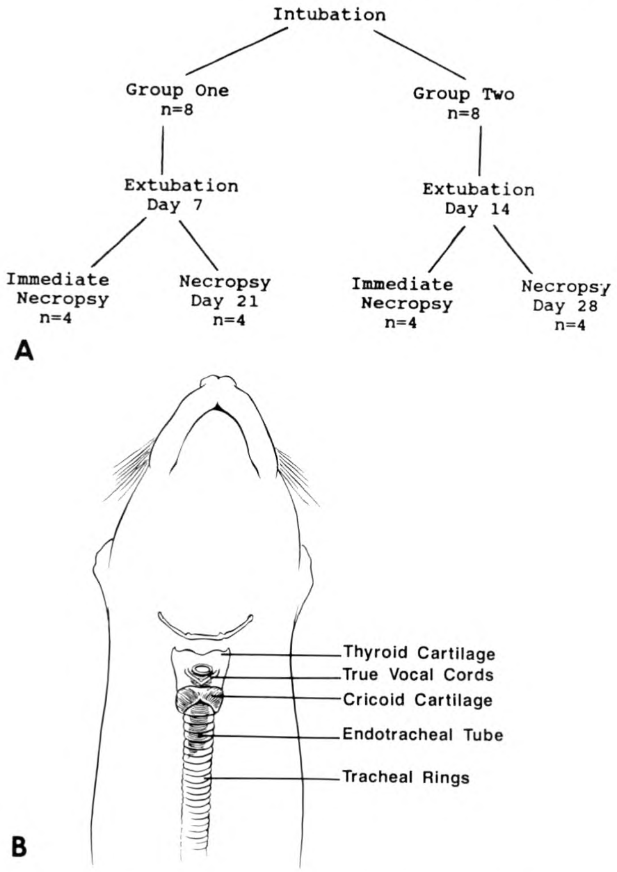


Fig 1. Experimental design. A) Duration of intubation for 16 ferrets. B) Sketch showing placement of endotracheal tube segment in laryngotracheal complex. Tube is secured in place with transcutaneous, transtracheal suture (not shown).

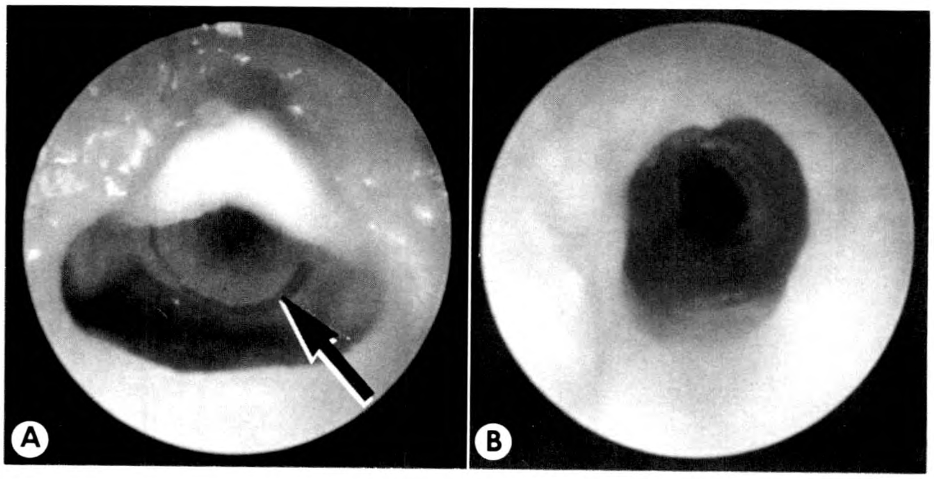
METHODS

Sixteen 8- to 10-week-old ferrets weighing between 440 and 550 g were obtained from Marshall Farms, North Rose, NY. All animals were vaccinated for canine distemper and placed on a diet of water and dry cat food for 1 week.

All ferrets were assigned randomly into two groups (Fig 1A) and intubated in the following manner. Ketamine hydrochloride (25 mg/kg) and xylazine (4 mg/kg) were administered intramuscularly and induced prompt surgical anesthesia. The larynx was visualized directly, and 1% topical lidocaine hydrochloride was applied for supplemental anesthesia. The airway then was intubated with the distal 3.5 cm of a noncuffed polyvinylchloride endotracheal tube measuring 3.5 mm in diameter (Fig 1B). The cephalic end of the tube was positioned precisely 2 to 3 mm above the glottis. Pilot studies revealed that more cephalic placement of the tube resulted in severe aspiration, while more caudal placement caused glottic trauma and in some cases airway obstruction from exuberant granulation tissue. The tube was secured in this position by a single 4-0 nylon transcutaneous, transtracheal retention suture. This suture was placed by direct visualization after aseptically preparing the cervical skin with povidone-iodine, vertically incising over the easily palpable cricoid cartilage and upper tracheal rings, and bluntly exposing the laryngotracheal complex. Direct laryngoscopy (Fig 2A) confirmed both proper position of the tube and intraluminal placement of the retention suture. The skin was closed with 5-0 chromic gut, and the retention suture was secured over a small button of folded sterile aluminum foil. All animals were given perioperative intramuscular benzathine penicillin (200,000 units), and this dose was repeated every third day postoperatively.

The animals in each group were weighed daily and closely monitored for signs of dehydration, weight loss, and aspiration. Initially all animals coughed and aspirated minor amounts. However, only profound weight loss and dehydration required premature extubation. The animals were extubated after either a 1- or 2-week period. Half of the animals in each group were killed immediately (by painless infusion of Euthol, 2 mL/kg) to look for acute changes in the airway, and the remaining animals underwent necropsy after an additional 2-week period that allowed time for maturation of the airway injury.

Fig 2. Endoscopic views. A) Of intubated ferret larynx. Arrow — cephalic end of 3.5-mm endotracheal tube positioned 2 to 3 mm above glottis. B) Of ferret subglottis postextubation (group 1, day 7). Note mucosal irregularity, diffuse edema, and narrowing. Photograph was taken with use of 2.8-mm 0° Hopkins telescope with tip of telescope just below vocal cords.



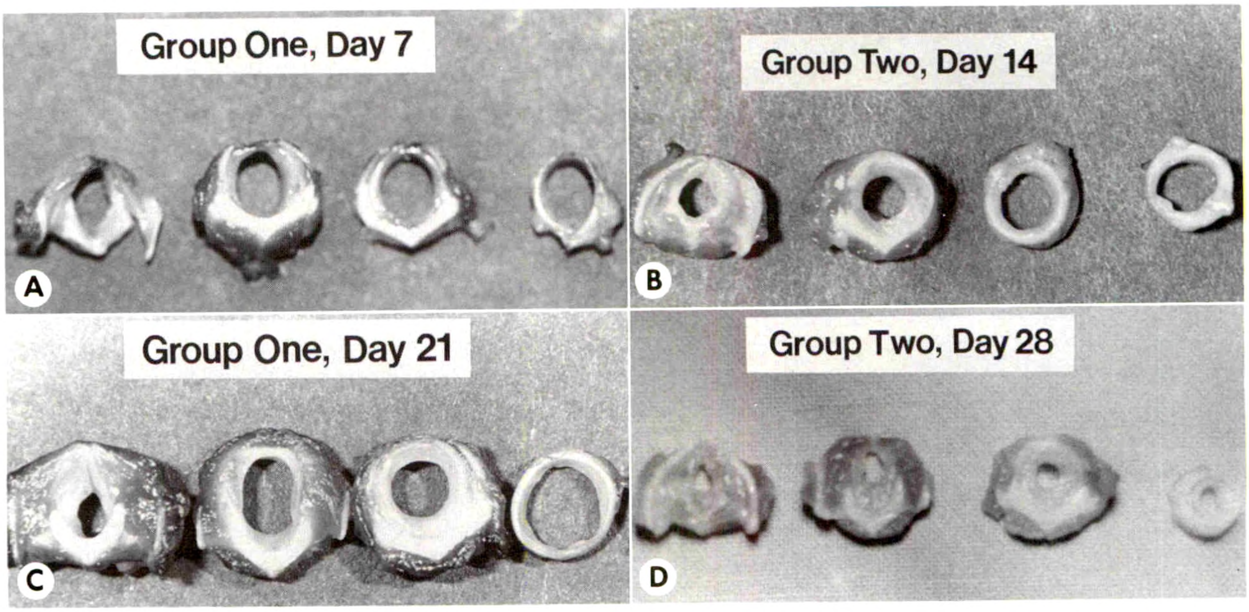


Fig 3. Serial horizontal sections through laryngotracheal complex. A) Subglottis is minimally narrowed by diffuse soft tissue edema following 7 days of intubation. B) Subglottis is narrowed considerably more after 2-week period of intubation. C) Resolution of acute subglottic injury 2 weeks after intubation for 7 days, with minimal residual subglottic stenosis. D) Progression and maturation of subglottic injury 2 weeks after intubation for 14 days, with marked reduction in subglottic lumen.

The degree of subglottic injury was ascertained first by inspecting the airway with use of a 2.8-mm 0° Hopkins telescope made by Karl Storz (Fig 2B). The gross appearance of the mucosa was noted, and the percentage of subglottic stenosis visually estimated. Serial sections of the laryngotracheal complex were obtained at the time of necropsy (Fig 3) for additional analysis. The specimens were fixed in formaldehyde and submitted for gross and histologic inspection. Prior to fixation, the section of each specimen through the cricoid lamina was photographed (Kiron 105-mm Macro Lens with a magnification ratio of 1:1). Photographic prints (20 x 27.5 cm [8 x 10 in]) were the means of performing computerized polar planimetry (Bioquant System IV software, SummaSketch Plus digitizer, IBM PC) to calculate the actual area (mm^2) of subglottic stenosis (Fig 4). This area of subglottic stenosis then was expressed as a percentage of the cross-sectional area at this level.

RESULTS

Group 1. All of the animals in group 1 developed a mild to moderate amount of subglottic stenosis, as seen in Table 1. At the end of the 7-day period of intubation, the subglottic mucosa endoscopically appeared hyperemic and irregular, with focal areas of ulceration (Fig 2B). There was a mild mucopurulent exudate. These gross findings correlated with those of the microscopic examination, which showed an inflammatory infiltrate into the submucosal layer centering around the areas of ulceration. There was no evidence of significant perichondritis or damage to the cartilaginous structures. When four animals in group 1 were examined on day 21 (necropsy 2 weeks postextubation), three of the four had begun to show resolution of their soft tissue stenosis (Fig 3A,C). Histologically there was mild squamous metaplasia in the respiratory epithelium lining the airway, but the soft tissue swelling and inflammatory infiltrate in the submucosal layer were less dense. The fourth animal showed evidence of a more chronic inflammatory reaction and had the most residual stenosis grossly. None of the animals in group 1 showed clinical evidence of respiratory distress.

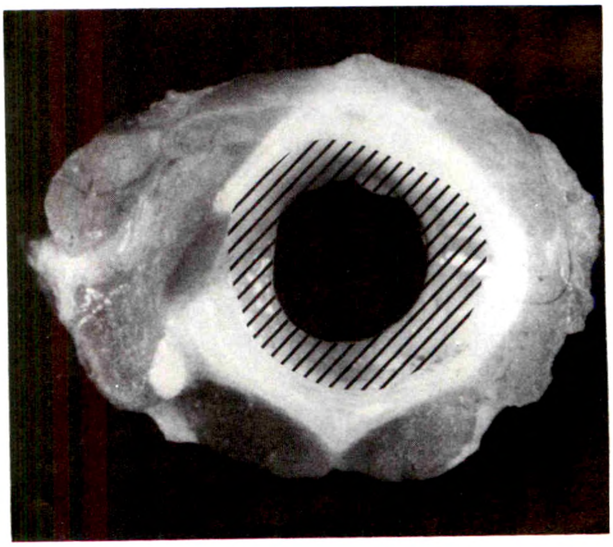


Fig 4. Photograph of ferret airway through cricoid lamina. Cross-hatching represents area (mm^2) of subglottic stenosis calculated by use of computerized polar planimetry. This area was expressed as percentage of cross-sectional area of airway at this level.

TABLE 1. PERCENTAGE OF ACQUIRED SUBGLOTTIC STENOSIS AS CALCULATED BY COMPUTERIZED POLAR PLANIMETRY

	Group 1		*Group 2*	
	Day 7	*Day 21*	*Day 14*	*Day 28*
	38%	39%	57%	59%
	58%	60%	43%	85%
	47%	37%	64%	44%
	60%	41%	56%	66%
Mean	51%	44%	55%	63%
Range	37%-85%			

$$\text{Subglottic stenosis} = \frac{\text{cricoid area (mm}^2) - \text{airway luminal area (mm}^2)}{\text{cricoid area (mm}^2)} \times 100$$

Group 2. All of the animals in group 2 developed a moderate amount of subglottic stenosis. But in contrast to group 1, the injury was of a more chronic variety and seemed to mature with time. As can be seen in Fig 3B, there was more gross evidence of soft tissue swelling and narrowing of the airway after this 2-week period of intubation. The amount of stenosis actually may have been restricted by the stenting effect of the endotracheal tube. Endoscopically, there was soft granulation tissue lining the airway, with a diffuse mucopurulent exudate. Microscopically (Fig 5), there again was mucosal ulceration evident, but with a denser inflammatory infiltrate and early organization of the connective tissue stroma. There was also evidence of perichondritis, and occasionally cysts were seen within the soft tissue stenosis. As can be seen in Table 2, the average amount of subglottic stenosis in the animals in group 2 increased with time from 55% to 63%. Grossly, this was evident by the moderate and in one case severe stenosis of the subglottic airway seen in the animals extubated for 2 weeks prior to necropsy (Fig 3D). Clinically, the animal with severe stenosis was showing signs of increasing respiratory distress at the time of necropsy. Histologically (Fig 6), there was evidence of a maturing chronic fibrosis.

DISCUSSION

The ferret model for acquired subglottic stenosis following prolonged endotracheal intubation herein described mimics the actual pathophysiology that occurs in humans. This pathophysiologic process has been investigated and previously reported in the literature.[21-24] In the ferret, intubation with a modified noncuffed endotracheal tube for 7 days produces a soft, usually reversible stenosis in the subglottis and trachea. Intubation for at least 14 days causes the acute airway injury to progress in a predictable fashion, ultimately resulting in a mature, nonreversible subglottic stenosis. Unlike histologic changes seen in traumatized rabbit airways,[25] there is no evidence of early ectopic cartilage formation in the subglottic fibrous tissue of the ferret. The initial pilot studies using the ferret model failed to show a more substantial subglottic stenosis when intubation exceeded 14 days; this finding is similar to that reported by Supance et al[18] for the canine model. Other pilot studies with this ferret model also failed to show that a more traumatic initial airway insult, such as intubation with a fiberglass test

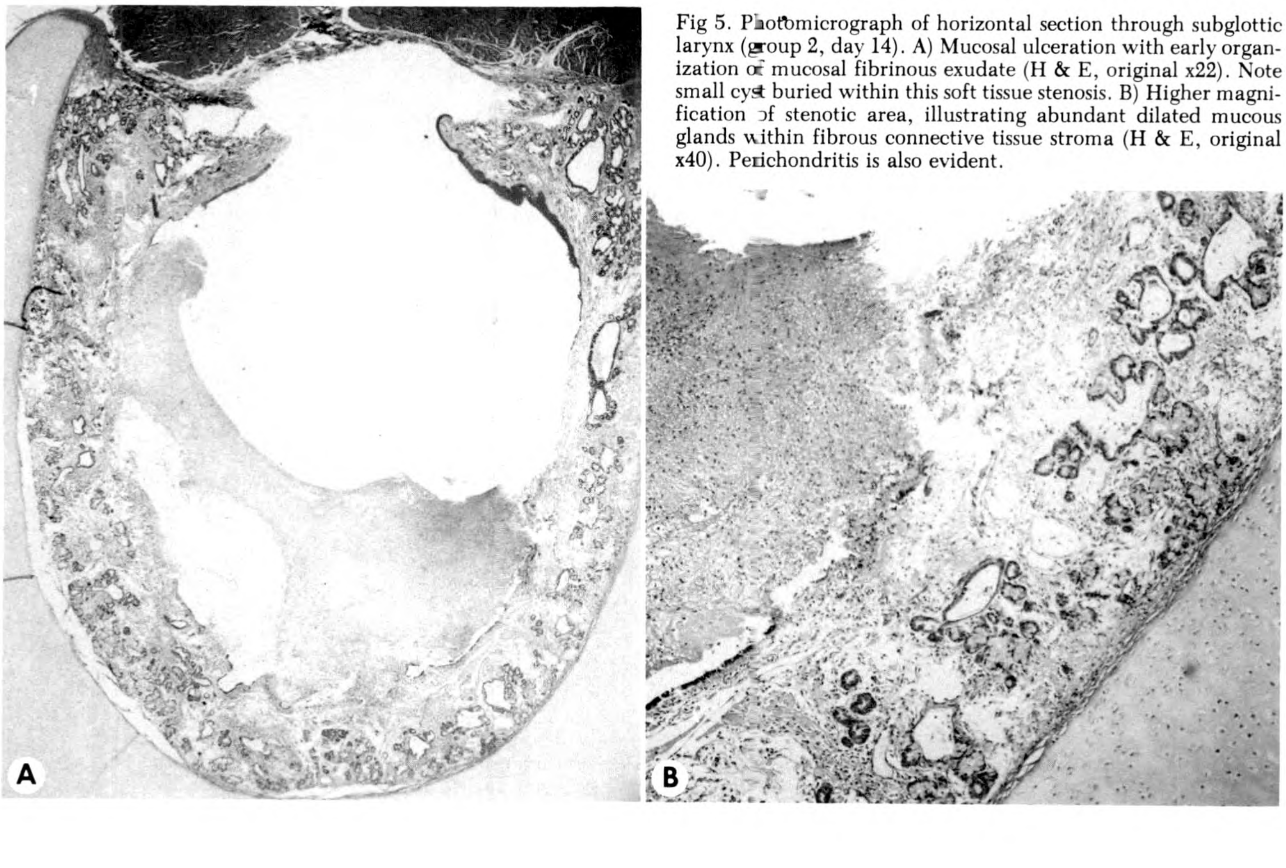


Fig 5. Photomicrograph of horizontal section through subglottic larynx (group 2, day 14). A) Mucosal ulceration with early organization of mucosal fibrinous exudate (H & E, original x22). Note small cyst buried within this soft tissue stenosis. B) Higher magnification of stenotic area, illustrating abundant dilated mucous glands within fibrous connective tissue stroma (H & E, original x40). Perichondritis is also evident.

TABLE 2. SUMMARY OF RESULTS

Group	*Day*	*Microscopic Findings*	*Average Subglottic Stenosis*
1	7	Submucosal inflammatory infiltrate, edema, mucosal ulceration	51%
1	21	Squamous metaplasia, resolution of soft tissue stenosis	44%
2	14	Severe mucosal ulceration, marked inflammatory infiltrate with early fibrous organization, perichondritis, occasional submucosal cysts	55%
2	28	Maturing fibrosis	63%

tube brush, would shorten the intubation time needed to cause a significant subglottic stenosis. The results of this study demonstrate that the duration of intubation in this ferret model for acquired subglottic stenosis is at least as important, if not more so, than an initial traumatic insult to the airway.

Pilot studies also were done to determine the feasibility of a tubeless tracheotomy in the ferret, in a manner similar to that described by Hansen[26] in the cat. Although it was possible to induce near-total subglottic stenosis above the stoma, the tubeless tracheotomy was not tolerated by the ferrets, with a perioperative mortality of 50% to 75% from tracheal mucous plugs in spite of humidification and suctioning three times per day.

The perioperative mortality in the ferret model using only prolonged endotracheal intubation to induce the subglottic injury was, however, less than 5%. In addition to the original 16 animals reported in this study, the authors subsequently have used this model with an additional 24 animals, and only one animal has died, of massive emesis and subsequent aspiration. Although all the animals initially aspirated and lost weight, most learned to swallow around the cephalic portion of the endotracheal tube, and only three required early extubation because of severe dehydration, weight loss, or sepsis. All three of these animals ultimately survived.

Although this ferret model may not be good for reconstructive procedures requiring a tracheotomy, it offers advantages over other animal models when used for procedures not requiring a tracheotomy, such as anterior and posterior cricoid split and long-term stenting. Its advantages over the traditional canine model include a substantial cost savings with regard to purchase price and housing. Because of their relatively small size, large numbers of ferrets can be housed and maintained easily in limited laboratory space.[27] The ferret is also quite easy to handle and anesthetize. There were no anesthetic-related complications in this study. That the ferret is readily available from breeders in a uniform size, age, and sex eliminates several variables encountered when working with mongrel dogs. The disproportionately large airway makes the ferret a particularly well-suited animal for the study of acquired subglottic stenosis and subsequent surgical therapy.

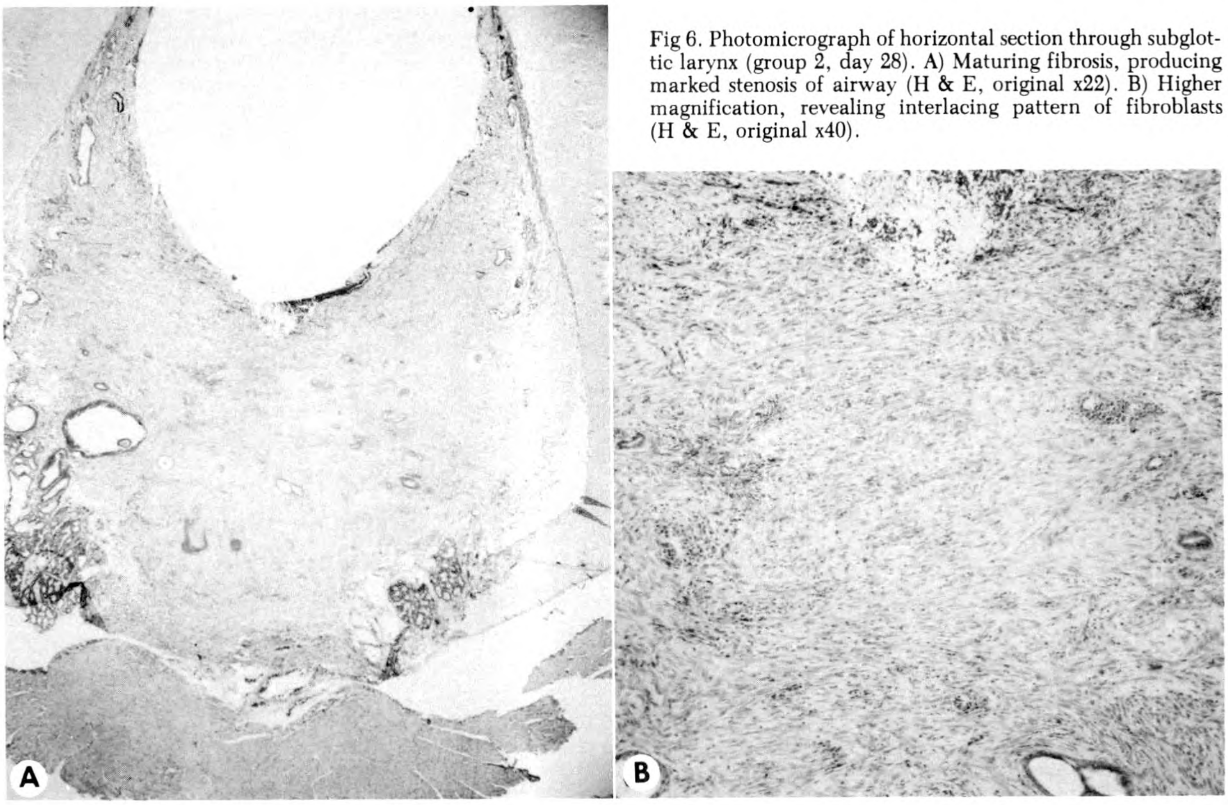


Fig 6. Photomicrograph of horizontal section through subglottic larynx (group 2, day 28). A) Maturing fibrosis, producing marked stenosis of airway (H & E, original x22). B) Higher magnification, revealing interlacing pattern of fibroblasts (H & E, original x40).

REFERENCES

1. Nau TW, Gates GA, Escobedo MB. Management of neonatal subglottic stenosis. Otolaryngol Clin North Am 1986;19:153-61.

2. Papsidero MJ, Pashley NRT. Acquired stenosis of the upper airway in neonates. An increasing problem. Ann Otol Rhinol Laryngol 1980;89:512-4.

3. Dankle SK, Schuller DE, McLead RE. Prolonged intubation of neonates. Arch Otolaryngol Head Neck Surg 1987;113:841-3.

4. Gilmore BB, Mickelson SA. Pediatric tracheotomy: controversy in management. Otolaryngol Clin North Am 1986;19:141-51.

5. Wetmore RF, Handler DS, Potsic WP. Pediatric tracheostomy. Experience during the past decade. Ann Otol Rhinol Laryngol 1982;91:628-32.

6. Healy GB. An experimental model for the endoscopic correction of subglottic stenosis with clinical applications. Laryngoscope 1982;92:1103-15.

7. Koufman JA, Thompson JN, Kohut RI. Endoscopic management of subglottic stenosis with the CO2 surgical laser. Otolaryngol Head Neck Surg 1981;89:219-20.

8. Goode RL, Shinn JB. Long-term stenting in the treatment of subglottic stenosis. Ann Otol Rhinol Laryngol 1977;86:795-8.

9. Schuller DE. Long-term stenting for laryngotracheal stenosis. Ann Otol Rhinol Laryngol 1980;89:515-20.

10. Sullivan MJ, McClatchey KD, Passemen PP. Airway growth following cricotracheal resection in puppies. Arch Otolaryngol Head Neck Surg 1987;113:606-11.

11. Cotton RT, Seid AB. Management of the extubation problem in the premature child. Anterior cricoid split as an alternative to tracheotomy. Ann Otol Rhinol Laryngol 1980;89:508-11.

12. Holinger LD, Stankiewicz JA, Livingston GL. Anterior cricoid split: the Chicago experience with an alternative to tracheostomy. Laryngoscope 1987;97:19-24.

13. Ochi JW, Seid AB, Pransky SM. An approach to the failed cricoid split operation. Int J Pediatr Otorhinolaryngol 1987;14:229-34.

14. Maddalozzo J, Holinger LD. Laryngotracheal reconstruction for subglottic stenosis in children. Ann Otol Rhinol Laryngol 1987;96:665-9.

15. Strome M, Norris CM, Brodsky G, Joseph MP, Eavey RD. An assessment of grafts in the posterior cricoid lamina. Laryngoscope 1982;92:1120-5.

16. Schuller DE, Parrish RT. Reconstruction of the larynx and trachea. Arch Otolaryngol Head Neck Surg 1988;114:278-86.

17. Cotton RT. Pediatric laryngotracheal stenosis. J Pediatr Surg 1984;19:699-704.

18. Supance JS, Reilly JS, Doyle WJ, Bluestone CD, Hubbard J. Acquired subglottic stenosis following prolonged endotracheal intubation: a canine model. Arch Otolaryngol 1982;108:727-31.

19. Woods CL, Postma DS, Prazma J, Sidman J. Effects of dexamethasone and oxymetazoline on "postintubation croup": a ferret model. Otolaryngol Head Neck Surg 1987;96:554-8.

20. Vinegar A, Sinett EE, Kosch AC, Miller ML. Pulmonary physiology of the ferret and its potential as a model for inhalation toxicology. Lab Anim Sci 1985;35:246-50.

21. Whited RE. A prospective study of laryngotracheal sequelae in long-term intubation. Laryngoscope 1984;94:367-77.

22. Sasaki CT, Hovich M, Koss N. Tracheotomy-related subglottic stenosis: bacteriologic pathogenesis. Laryngoscope 1979;89:857-65.

23. Borowiecki B, Croft CB. Experimental animal model of subglottic stenosis. Ann Otol Rhinol Laryngol 1977;86:835-40.

24. Bishop MJ. Laryngeal injury in a dog model of prolonged endotracheal intubation. Anesthesiology 1985;62:770-3.

25. Adriaansen FCPM, Verwoerd-Verhoef HL, Heul RO, Verwoerd CDA. A histologic study of the growth of the subglottis after endolaryngeal trauma. Int J Pediatr Otorhinolaryngol 1986;12:205-15.

26. Hansen DG. Technique for long-term feline tracheostomy. Arch Otolaryngol 1983;109:400-2.

27. Moody KD, Bowman TA, Lang CM. Laboratory management of the ferret for biomedical research. Lab Anim Sci 1985;35:287-90.

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IMAGING CASE STUDY OF THE MONTH

COMPUTED TOMOGRAPHY OF THE HYPOPLASTIC MAXILLARY SINUS

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INTRODUCTION

Maxillary sinus opacity is a common plain film finding produced by many entities. Some of the abnormalities could be identified on the plain film examination.

Computed tomography and magnetic resonance imaging may aid definitive diagnosis of the cause of maxillary sinus opacity. To illustrate this concept, CT findings in a patient with maxillary sinus opacity due to sinus hypoplasia will be shown and discussed.

CLINICAL FINDINGS

A 31-year-old woman presented with a sensation of "fullness" in the left maxillary sinus. This symptom disappeared with vasoconstrictor nasal medications.

A Waters view (see Figure, A) revealed a clear left maxillary sinus. Opacity of the right maxillary sinus prompted CT examination. The right orbit floor is much lower in position than the left.

COMPUTED TOMOGRAPHIC FINDINGS

The Figure, B-D, shows contiguous 5-mm thick axial sections of the maxillary sinuses. The lowest view, just above the alveolar area, shows a small, round sinus space anteriorly with a long bony ostium extending to the middle meatus (see Figure, B). The sinus space has a normal mucoperiosteal border. Posteriorly, intramedullary bone is present between the sinus and the pterygopalatine fissure.

The next higher CT layer shows communication between the sinus ostium and the middle meatus (see Figure, C). This is the most medial portion of the ostium lying in continuity with the lower slice. Slight widening of the nasal fossa transverse dimension is present compared to the left side.

The highest view (see Figure, D) is just below the orbit floor. This shows the greatest widening of the nasal fossa. The middle meatus is also wider than on the opposite side. Posteriorly, the pterygopalatine fossa is much larger on the right than on the left.

The Figure, E, is a coronal CT through the plane of the right sinus ostium and small sinus. This shows the small vertical sinus dimension on the right compared to the left. The canine recess is also very high in position on this side. The infraorbital canal is located lateral to the sinus cavity.

DISCUSSION

The main finding in maxillary sinus hypoplasia that may serve as a pitfall in diagnosis is sinus opacity. If one has only a plain film, the opacity may simulate a fluid- or tissue-filled sinus space. A CT examination would define better the true sinus content.

Similar diagnostic confusion may result from the eye position change produced by enlargement of the homolateral orbit in maxillary hypoplasia. Exophthalmos of the contralateral eye may be suggested by the posterior position of the eye on the side of maxillary sinus hypoplasia. Both enophthalmos and sinus opacity are clinical pitfalls connected with maxillary sinus hypoplasia and make recognition of the entity very important.

Karmody et al[1] presented their findings in respect to sinus hypoplasia. Among their 750 patients, 1.73% (13 patients) had unilateral hypoplasia. Bilateral hypoplasia was more common, being found in 7.2% (54 patients).

Proops[2] evaluated histologically the bone of the intramedullary area in two cases of sinus hypoplasia and found the bone was not abnormal. This author also mentioned fibrous dysplasia, Paget's disease, and osteoma as causes of sinus wall thickening that were not present in his cases.

Modic et al[3] reviewed three patients with unilateral maxillary sinus hypoplasia and described the basic findings in this process. These include low position of the orbit floor with an increased vertical orbit dimension on the involved side.[4] They also found an increase in the transverse width of the ipsilateral nasal fossa in their cases.

Bassiouny et al[5] described a higher incidence of unilateral maxillary sinus hypoplasia in their group

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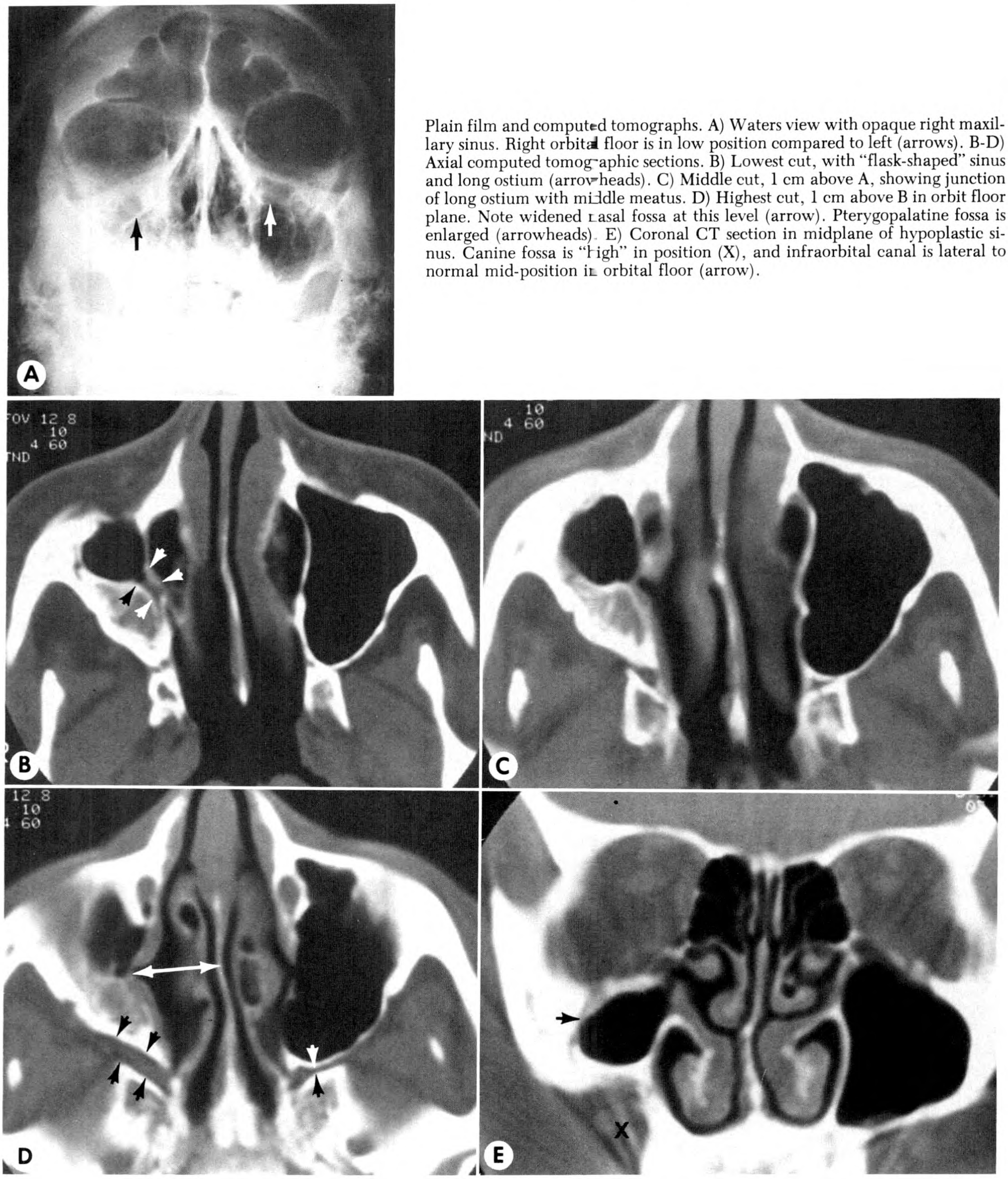

Plain film and computed tomographs. A) Waters view with opaque right maxillary sinus. Right orbital floor is in low position compared to left (arrows). B-D) Axial computed tomographic sections. B) Lowest cut, with "flask-shaped" sinus and long ostium (arrowheads). C) Middle cut, 1 cm above A, showing junction of long ostium with middle meatus. D) Highest cut, 1 cm above B in orbit floor plane. Note widened nasal fossa at this level (arrow). Pterygopalatine fossa is enlarged (arrowheads). E) Coronal CT section in midplane of hypoplastic sinus. Canine fossa is "high" in position (X), and infraorbital canal is lateral to normal mid-position in orbital floor (arrow).

of 500 patients. Eighteen patients (3.6%) had unilateral hypoplasia in their series. These authors also describe increased size of the superior orbital fissure in 36.1% of their patients with unilateral sinus hypoplasia.

Our patient had all of the above findings in her examination. The right canine fossa is elevated, and only the anterior portion of the maxilla is pneumatized. The sinus ostium is elongated and oblique in its course. Ipsilateral nasal fossa enlargement and a low-lying orbit floor with orbit enlargement in the vertical axis are present. The right superior fissure is enlarged.[5]

An additional finding not reported by other authors but present in this and other cases we have reviewed is enlargement of the pterygopalatine fossa due to a short anteroposterior length of the maxilla on the affected side. The pterygoid processes are normal in position. Another unreported finding present in our patient is the lateral location of the infraorbital neurovascular canal, which lies lateral to the hypoplastic air cell. These five findings constitute the complete diagnostic criteria of unilateral maxillary sinus hypoplasia:

1. Enlargement of vertical orbit.
2. Enlargement of superior orbital fissure.
3. Elevated canine fossa.
4. Enlargement of pterygopalatine fissure.
5. Lateral position of infraorbital neurovascular canal.

DIFFERENTIAL DIAGNOSIS

Bassiouny et al[5] also have proposed a classification of maxillary sinus hypoplasia. In the developmental category are:

1. Isolated hypoplasia, either primary or related to arrested development secondary to infection, trauma, or irradiation.
2. Regional developmental anomalies such as facial dysostosis.

In the acquired category are:

1. Hypoplasia due to a systemic disorder such as thalassemia or cretinism.
2. Trauma with deformity due to healing of a fracture or postoperative hypoplasia.
3. Inflammatory osteitis, best typified by the decreasing maxillary sinus size produced by Wegener's granulomatosis.
4. Neoplastic osteitis or osteoblastic metastasis.
5. Fibroproliferative abnormality such as fibrous dysplasia or Paget's disease.

Dysostosis should result in a bilateral decrease in maxillary sinus size. However, the degree of hypoplasia may be dissimilar on the two sides. Most of the acquired forms of hypoplasia really produce maxillary sinus wall thickening (blastic osteitis), so that the sinus air space is reduced while the overall size of the maxillary bone is normal or enlarged.

Rarely, the maxillary sinus may contain a septum that when one side of the maxillary cell is pneumatized and the second opaque may simulate hypoplasia. However, in this condition the overall size of the maxillary bone is normal in the cases we have reviewed.

REFERENCES

1. Karmody CS, Carter B, Vincent M. Development anomalies of the maxillary sinus. Trans Am Acad Ophthalmol Otolaryngol 1977;84:723-38.

2. Proops DW. The unilateral thick-walled antrum. J Laryngol Otol 1983;97:369-73.

3. Modic MT, Weinstein MA, Berlin J, Duchesneau PM. Maxillary sinus hypoplasia visualized with computed tomography. Neuroradiology 1980;135:383-5.

4. Bierny JP, Dryden R. Orbital enlargement secondary to paranasal sinus hypoplasia. Am J Roentgenol 1977;128:850-2.

5. Bassiouny A, Newlands WJ, Ali H, Zaki A. Maxillary sinus hypoplasia and superior orbital fissure asymmetry. Laryngoscope 1982;92:441-8.

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PATHOLOGY CONSULTATION

BASALOID-SQUAMOUS CARCINOMAS OF THE UPPER AERODIGESTIVE TRACTS

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Basaloid-squamous carcinoma is a new addition to the lexicon of variants of squamous cell carcinoma. The carcinoma is distinctive histologically, is biologically high grade, and manifests a predilection for the base of tongue, hypopharynx, and supraglottic larynx.

The most common malignancy in the head and neck is squamous cell carcinoma. The majority of these are of a conventional type, albeit with variable differentiation. Others are not so phenotypically homogeneous, and these variants can pose diagnostic and histogenetic problems: the former pragmatic, the latter hypothetical. Because of their departure from prototypic squamous cell carcinomas, the variants have acquired a separate and descriptive nomenclature: verrucous, sarcomatoid, nonkeratinizing, clear cell, adenoid, and adenosquamous carcinomas. A new addition to the group is the recently described basaloid-squamous carcinoma.

Characterized by Wain et al[1] as a distinct histopathologic entity in 1986, this infrequently encountered yet histologically distinctive carcinoma has likely been unrecognized or included in other variants of squamous cell carcinoma such as adenosquamous carcinoma. Besides its apparently sharp predilection for the base of tongue, the hypopharynx (particularly the pyriform sinus), and the supraglottic larynx (including the epiglottis), the importance of the recognition of the carcinoma is twofold. Basaloid-squamous carcinomas are biologically high grade, and because of their markedly divergent phenotypic expression, biopsy specimens may not be representative of the whole lesion.

As its name connotes, the carcinoma is distinguished by at least two cytomorphologic components (see Figure). In addition, the carcinoma manifests both deep and lateral invasion at the time of diagnosis. Since the basaloid-squamous carcinoma is a variably differentiated squamous cell carcinoma, that recognizable phenotype is, or should be, present. The squamous carcinoma is usually well to moderately well differentiated and invasive (see Figure, A). Six of the ten carcinomas described by Wain et al[1] and all five of the authors' cases showed this feature. Wain et al[1] have also described squamous cell carcinoma in situ as a finding. Three of our five cases have shown multifocal origin over a broad area of mucosa, and all five were deeply invasive into the seromucous gland layer or skeletal muscle. Invasion is by the squamous or basaloid component or both.

It is, however, the basaloid component that sets the carcinoma apart. The growth pattern of the basaloid cells is often lobular, but can be in cords or trabeculae (see Figure; C,D). Hyperchromatism is imparted by the small, often closely apposed cells and dark nuclei. The nuclei also can be large and vesicular. Central necrosis, a hyalomucoid stroma and ribbon, or cystic, glandlike spaces completes the diversity of expression. The bulk of the basaloid component may not have a unity with either the squamous carcinoma component or the surface mucosa, but where this is present it is unequivocal (see Figure, E).

A sampling deficiency of biopsy may not provide a specimen with both components of the carcinoma. Without the squamous cell carcinoma features, a submucosal salivary gland neoplasm (pertinently high-grade adenoid cystic carcinoma) or a neuroendocrine carcinoma is suggested.

Electron optic study of the basaloid cells has demonstrated few organelles other than desmosomes, rare tonofilaments, and free ribosomes.[1] Granules, neurosecretory or otherwise, have not been identified.

There is no question that basaloid-squamous carcinoma is an aggressive malignancy. Six of the ten patients reported by Wain et al[1] had metastases to cervical lymph nodes at the time of initial surgery. Distant metastases were present in four, and two others developed distant spread (lungs, bones, or multiple). The carcinomas can be rapidly lethal. Three of the four deaths reported by Wain et al[1] occurred within 1 year of primary surgery.

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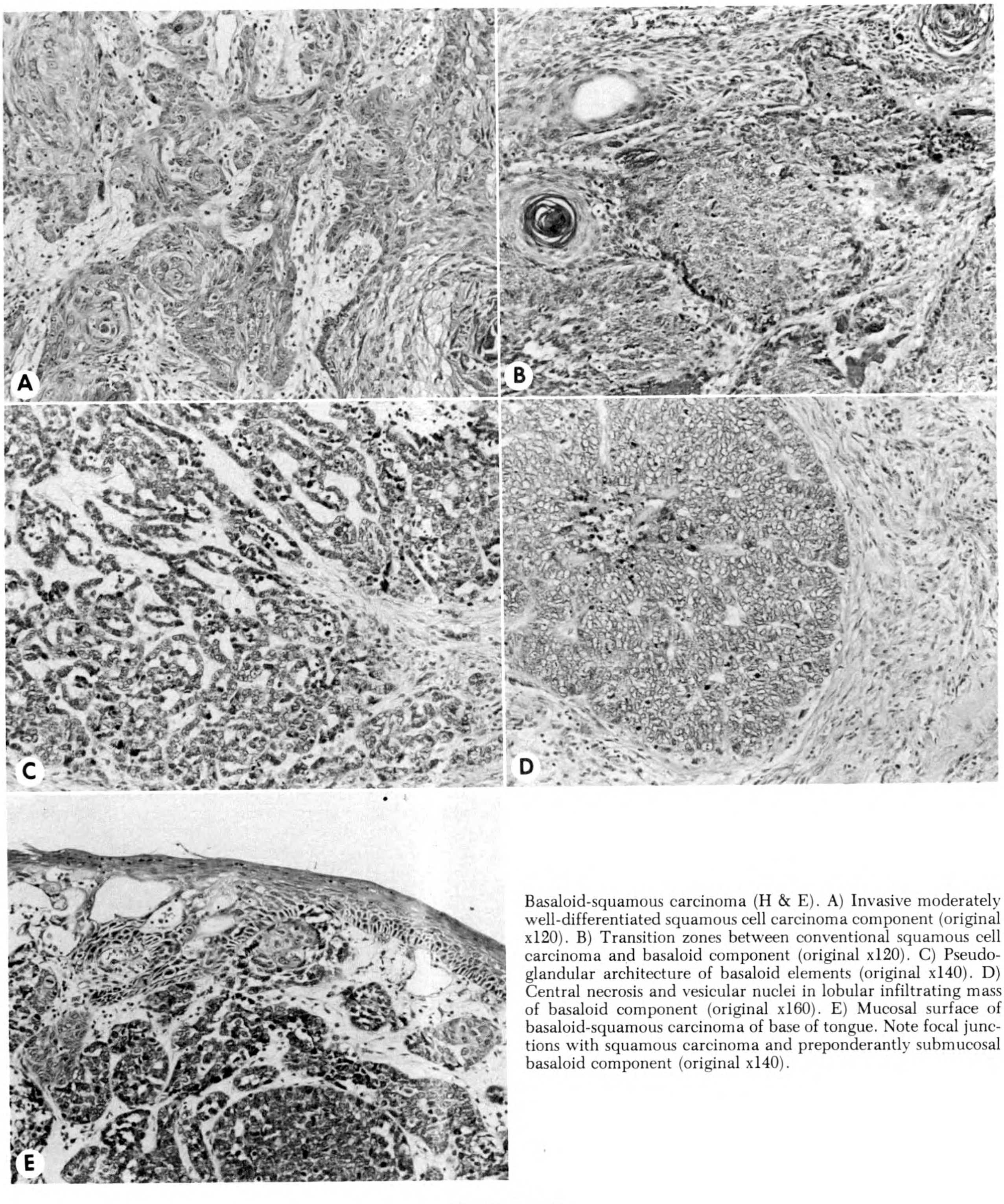

Basaloid-squamous carcinoma (H & E). A) Invasive moderately well-differentiated squamous cell carcinoma component (original x120). B) Transition zones between conventional squamous cell carcinoma and basaloid component (original x120). C) Pseudoglandular architecture of basaloid elements (original x140). D) Central necrosis and vesicular nuclei in lobular infiltrating mass of basaloid component (original x160). E) Mucosal surface of basaloid-squamous carcinoma of base of tongue. Note focal junctions with squamous carcinoma and preponderantly submucosal basaloid component (original x140).

REFERENCE

1. Wain SL, Kier R, Vollmer RT, Bossen EH. Basaloid-squamous carcinoma of the tongue, hypopharynx, and larynx: report of 10 cases. Hum Pathol 1986;17:1158-66.

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ANNALS

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STERNOMASTOID TUMOR OF INFANCY

APPLICATIONS OF THE VOICE PROSTHESIS DURING LARYNGECTOMY

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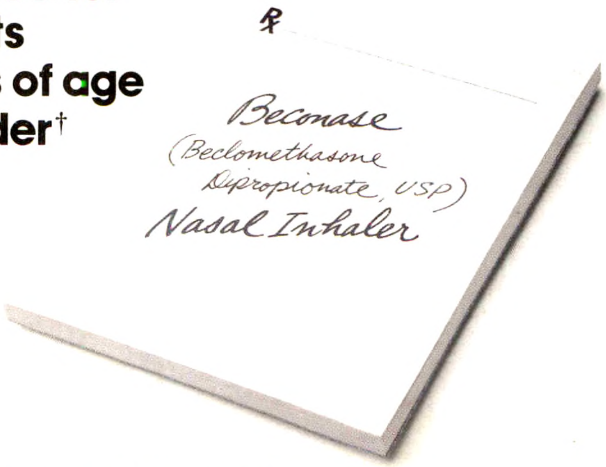

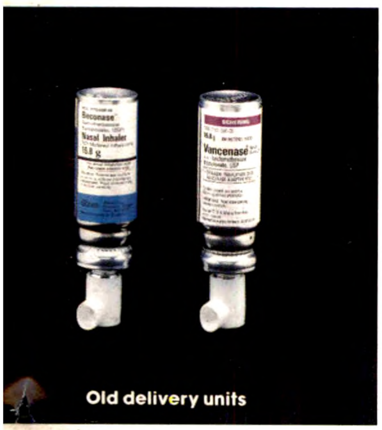

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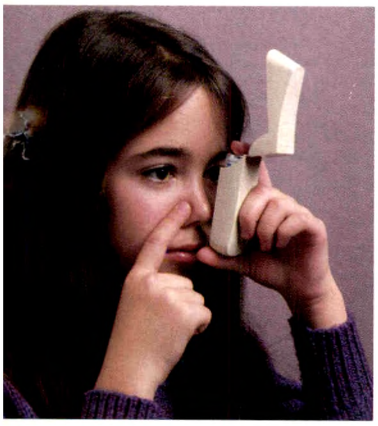

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Please consult Brief Summary of Prescribing Information on the following page.

References: 1. Meltzer EO, Busse WW, Bush RK, et al: Beclomethasone dipropionate nasal aerosol spray in allergic rhinitis: A comparison of three delivery systems. *Ann Allergy* 1985;55:802-804. 2. Data on file, Glaxo Inc.

Printed in USA

March 1989

BECONASE® Nasal Inhaler **BRIEF SUMMARY**
(beclomethasone dipropionate, USP)
For Nasal Inhalation Only

The following is a brief summary only. Before prescribing, see complete prescribing information in BECONASE® Nasal Inhaler product labeling.

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with BECONASE® Nasal Inhaler can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to BECONASE Nasal Inhaler. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate-day prednisone systemic treatment and orally inhaled beclomethasone increases the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, BECONASE Nasal Inhaler treatment should be used with caution in patients already on alternate-day prednisone regimens for any disease.

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PRECAUTIONS: General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude, and depression.

Extremely rare instances of nasal septum perforation and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuation of treatment with BECONASE® Nasal Inhaler.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of BECONASE Nasal Inhaler may suppress HPA function.

BECONASE Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

For BECONASE Nasal Inhaler to be effective in the treatment of nasal polyps, the aerosol must be able to enter the nose. Therefore, treatment of nasal polyps with BECONASE Nasal Inhaler should be considered adjunctive therapy to surgical removal and/or the use of other medications which will permit effective penetration of BECONASE Nasal Inhaler into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using BECONASE Nasal Inhaler over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septum ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

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Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1,000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when BECONASE Nasal Inhaler is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below 6 years of age have not been established.

ADVERSE REACTIONS: Side effects reported are primarily associated with the nasal mucous membranes. They include sensations of irritation and burning in the nose (11 per 100 patients) and occasional sneezing attacks (10 per 100 adult patients), which immediately follow the use of the intranasal inhaler. Localized infections of the nose and pharynx with *Candida albicans* have occurred rarely. Transient episodes of epistaxis have been reported in 2 per 100 patients, and ulceration of the nasal mucosa has been reported rarely. Extremely rare instances of nasal septum perforation and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation of beclomethasone. If recommended doses are exceeded or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's syndrome, could occur.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

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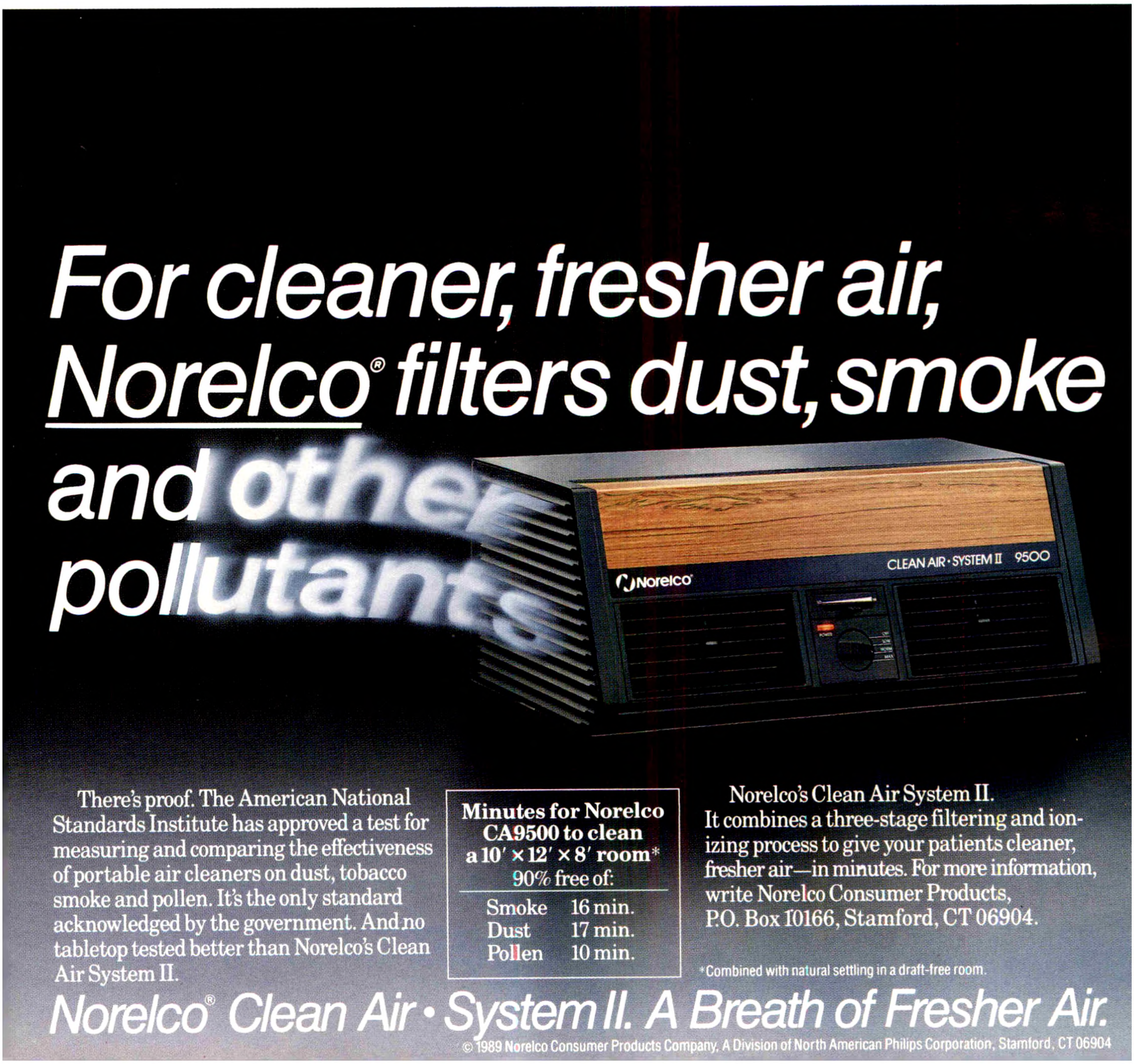
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APPLICATIONS OF THE VOICE PROSTHESIS DURING LARYNGECTOMY

MARK I. SINGER, MD
ERIC D. BLOM, PHD
RONALD C. HAMAKER, MD
GLEN Y. YOSHIDA, MD

INDIANAPOLIS, INDIANA

With the recent introduction of the voice prosthesis for alaryngeal speech rehabilitation, its application in the early postlaryngectomy period is gaining acceptance. One hundred twenty-eight patients received a tracheoesophageal puncture and adjunctive pharyngeal constrictor relaxation during laryngectomy. The voice prosthesis was applied as early as 10 days after surgery, and the results of a 9-year experience are presented. Eighty percent of the population achieved a durable voice, and the complications were infrequent. The results support the primary use of tracheoesophageal phonation as a relatively safe and reliable alternative to total laryngectomy alone.

KEY WORDS — laryngectomy, pharyngeal constrictor myotomy, pharyngeal plexus neurectomy, tracheoesophageal puncture, voice prosthesis, voice restoration.

Voice restoration after total laryngectomy is an operative challenge paralleling the development and refinement of the treatment for laryngeal carcinoma. A large number of procedures have been proposed over the last 50 years to enhance the rapid development of alaryngeal speech. All of the procedures divert expired air into the pharynx or esophagus, with variations in the shunt lining and connection to the trachea.[1] Pharyngoesophageal insufflation produces mucosal vibration and sound in the residual vocal tract. The articulatory structures for voice refine the sound into understandable and natural speech. The shunt procedures are relatively simple to perform and allow for rapid speech rehabilitation. The voice prosthesis introduced by the authors effectively prevents pharyngoesophageal contents from soiling the airway with long-term shunt use.[2]

A recent workshop dedicated to speech rehabilitation following laryngectomy was held at The Johns Hopkins Hospital, where Johns and Myers[3] stated: "Surgical approaches for voice restoration have undergone an enormous evolution over the past 10 years: from the point where esophageal speech was the standard and a variety of reconstructive surgical procedures were available (none of which was terribly effective) to the present where the tracheoesophageal puncture (TEP), is considered to be state-of-the-art."

Ward et al[4] stated: "Tracheoesophageal voice fistula techniques have withstood the test of time for some 9 years; however, they are not without complications. Successful speech rehabilitation in the laryngectomy patient with TEF is reported by some authors to be 80%-90%."

There has been some concern by laryngologists that a tracheoesophageal puncture (TEP) or "prosthetic" speech restoration for the laryngectomized may deter the development of improved conservation laryngectomy procedures. This has not occurred, but TEP has provided an alternative to partial laryngectomy and its limitations. Recently, "near-total laryngectomy" procedures have been introduced, but they should not be considered extensions of the conservation techniques, and results reporting must be directed to cancer treatment and airway protection.[5]

The initial introduction of TEP procedures was intended to present an effective and relatively safe voice restoration technique after laryngectomy and alaryngeal speech failure. At that time, in 1978, the "neoglottic" techniques for laryngectomy with immediate voice restoration were popularized by Staffieri.[6] Unsatisfactory experience with the neoglottis had accumulated by this time, and it was apparent that the application of the voice prosthesis to an immediate TEP during laryngectomy might provide a reliable alternative approach. The following report presents the results of a series of primary voice restorations started in 1979. The observations and results were analogous to the experience with secondary voice restoration.[7,8] The operative technique has changed as experience was gained with tracheoesophageal phonation and the problems it introduced. The techniques represent little alteration of the conventional total laryngectomy and no anticipated change in the results of treatment.

MATERIALS AND METHODS

The series represents 128 patients treated by total laryngectomy and TEP placed primarily. The ratio of men to women is 97:31. The age range is 37 to 80 years. Adjunctive treatment included radiation therapy in 96 cases, 56 preoperative and 40 postoperative. Table 1 describes the case distribution by

---

From Head and Neck Surgery Associates, Indianapolis.

Presented at the meeting of the American Laryngological Association, San Francisco, April 1-2, 1989.

REPRINTS — Mark I. Singer, MD, Medical Tower Inn No. 780, 1633 N Capitol Ave, Indianapolis, IN 46202.

TABLE 1. STAGE AND SITE OF LESION

	Stage				
	II	*III*	*IV*	*Recurrent*	*Total*
Site					
Glottic	6	13	19	18	56
Supraglottic	6	7	14	1	28
Subglottic	1				1
Pharyngeal	3	1	1		5
Pyriform sinus	4	10	14	3	31
Oral cavity		1	1	2	4
Thyroid		1			1
Cricoid			1		1
Chronic aspiration					1
Total	20	33	50	24	128

No stage I tumors were treated.

stage and location. One case of aspiration control after supraglottic laryngectomy was included. Another case of chondrosarcoma of the cricoid cartilage and one of invasive papillary carcinoma of the thyroid were included also.

The operative technique includes four procedures planned to reduce complications and to promote effective long-term use of the voice prosthesis. The first step requires construction of a durable tracheostoma with reduced tendency for stenosis and patency without a tracheal cannula. The tracheal ring is fixed to the inferior skin margin after defatting the tissues. A monofilament suture is placed around the tracheal ring and is secured by a vertical mattress technique. The posterolateral ring is incised bilaterally for a vertical distance of 1 cm (Fig 1). A triangular wedge of skin from the superior flap is interposed into the resulting defect to expand the area of the stoma as a "bivalving" technique. The membranous tracheal wall is closed with the overlying skin of the superior flap to produce a flat posterior stoma.

The TEP is placed by insertion of a right-angled hemostatic clamp through the unrepaired pharyngostoma until it distends the membranous wall from posterior to anterior. A No. 15 knife blade is used to transect the membranous trachea transversely for 3 to 4 mm in order to permit the tips of the hemostat to protrude into the tracheostoma (Fig 2). Care must be taken to prevent separation of the tracheoesophageal party wall. If this occurs, the hazard of salivary contamination increases, with subsequent development of infection and necrosis of the membranous trachea. The separation is repaired easily with two sutures placed bilaterally superior and inferior to the puncture from the membranous trachea to the anterior esophageal wall.

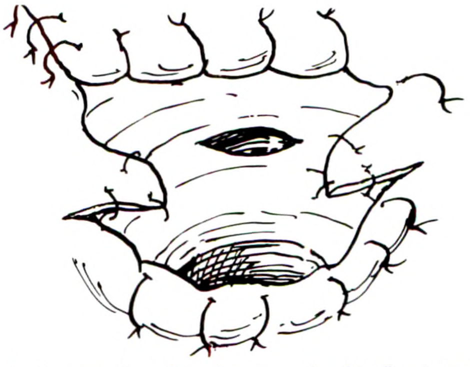

Fig 1. Construction of tracheostoma by skin flap interposition into bivalved trachea.

Observations of failed tracheoesophageal speakers led to the application of muscle-relaxing procedures to the pharyngoesophagus to avoid "spasm" and resultant dysfluency.[9] This involves either a pharyngeal constrictor myotomy or a pharyngeal plexus neurectomy. The myotomy technique consists of a posterior midline incision through the fibers of the middle pharyngeal constrictor muscle, the inferior pharyngeal constrictor muscle, and the cricopharyngeus muscle. A midline posterior approach is minimally traumatic and preserves the vascularity of the underlying mucosal segment while avoiding the possibility of re-formation of the upper esophageal sphincter. The myotomized constrictor muscles are available as a third-layer closure of the pharynx to support the anterior wall.

The more recently proposed pharyngeal plexus neurectomy offers a number of advantages over the myotomy. It reduces the trauma to the pharyngeal wall and the rise in sphincter tone of the upper esophageal segment during esophageal insufflation.[10] The elasticity of the constrictor muscles of the pharynx, as well as the vasculature, is preserved. These differences from myotomy were expected to decrease postoperative complications while preserving the quality of voice.

The pharyngeal plexus is identified on the ipsilateral laryngopharynx while the larynx is still intact.[11] The fibers are stretched and divided and the edges are electrocoagulated (Fig 3). This effectively denervates the inferior pharyngeal constrictor muscle and partially denervates the cricopharyngeus muscle.

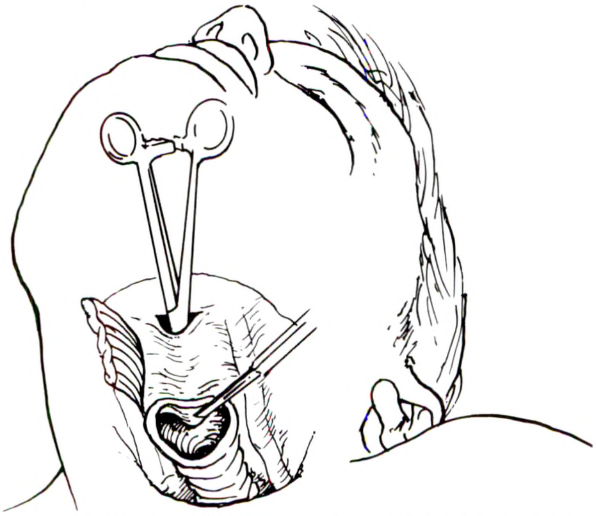

Fig 2. Technique of primary tracheoesophageal puncture.

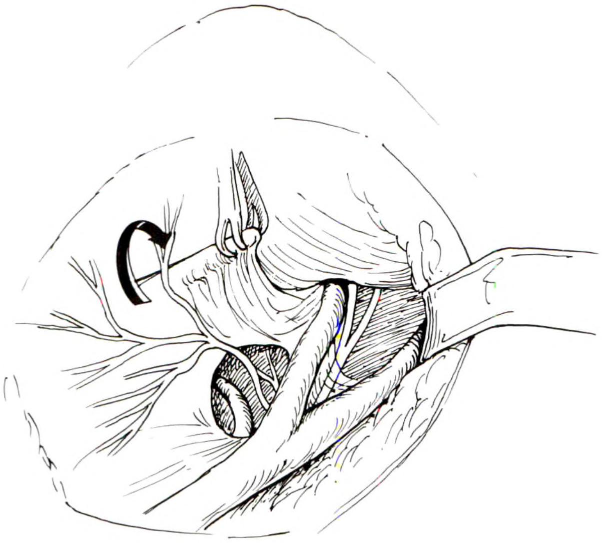

Fig 3. Surgical anatomy of pharyngeal plexus during neurectomy.

The laryngectomy is facilitated by a midline esophagotomy at the level of the cricoid. Scissors dissection is preferred, with one blade introduced to the lumen and the other held externally; the pharyngeal mucosa of the noninvolved side and the constrictor muscles are incised as a unit, in contrast to the well-known method of separating the constrictors at the oblique line of the larynx (Fig 4). The dissection is brought superiorly through the pyriform sinus, across the vallecula, and inferiorly through the opposite pyriform sinus. This approach spares the vascularity of the residual constrictor muscles for later pharyngeal closure.

The mucosal closure with use of a Connell suture technique to achieve a "Y" suture line provides minimal tension. The suture line is supported with a second, Lembert suture technique, which is followed with the buttress layer of the incised pharyngeal constrictors. When the residual pharyngeal remnant is less than 3 cm in transverse dimension, tissue augmentation with the pectoralis major myocutaneous flap is included. Twenty-nine of the 128 patients underwent flap interpositions, and one was reconstructed by free flap jejunal interposition.

When a patient resumes swallowing food, the voice prosthesis is placed in the TEP after removal of the feeding catheter-stent. The distance across the tracheoesophageal wall is measured and the appropriate length prosthesis is inserted. Voicing begins at the point of prosthesis insertion, and a training program for stomal hygiene and prosthesis care is started.

RESULTS

The effectiveness of the laryngectomy initially is gauged by its ability to control the cancer. The data collected over 9 years are displayed in two groups of 4-year periods. Long-term survivals are presented with shorter experience in the more current group. The disease-free incidences of the overall groups are as expected for stage III and IV populations; and the differences of 56% and 71% (Table 2) are more apparent than real, since the follow-up is shorter in the second group. The recurrence rates are within the expected range for this patient population, and the stoma recurrence of 3% to 4% is reasonable.

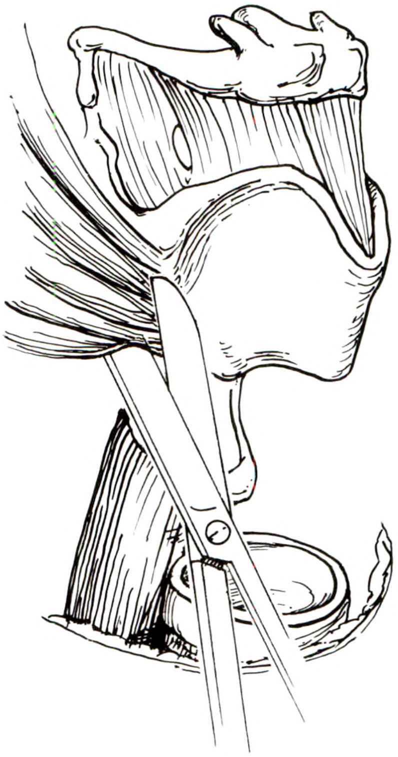

Fig 4. Laryngopharyngeal resection sparing pharyngeal constrictor muscles.

Voice failures are defined as failure to use the voice prosthesis for regular day-to-day communication. The first group of 48 patients had a failure rate of 29%; of these, eight patients were salvaged secondarily, for a long-term failure of 13%. The more current group failed 15% of the time, with five salvaged, for a persistent failure of 9%. This represents an improving trend for voice rehabilitation in the populations over the last 9 years that includes the development of better voice prostheses, more effective patient training, and refinement of the operative techniques. Speaking after primary voice restoration ranges from 10 to 35 days postoperatively, with an average of 22 days. Concomitantly, deglutition resumed 4 to 25 days postoperatively, with an average of 10 days.

Included in the voice failure group is a subpopulation of tracheoesophageal speech failures related to high pharyngeal resistance during insufflation for phonation.[9] Adding the pharyngeal constrictor myotomy or pharyngeal plexus neurectomy to the primary operative procedure, we experienced failure in 11 of 65 (17%) myotomized patients and

TABLE 2. LONG-TERM SURVIVAL AT 4 YEARS

	1979-1983		1984-1988	
	No.	%	No.	%
NED	27	56	57	71
DOD	20	42	16	20
Alive with disease	1	2	5	6
Died, second primary	0	0	2	3
Total	48		80	
Recurrence				
Local	4	8	5	6
Stomal	2	4	2	3
Regional	5	10	12	15
Distant	10	21	13	16

NED — no evidence of disease, DOD — dead of disease.

TABLE 3. TRACHEOESOPHAGEAL PUNCTURE COMPLICATIONS

	1979-1983	1984-1988
Stoma stenosis	4	1
TEP closure	13	4
Prosthesis extruded	5	2
Poor hygiene	3	1
Doesn't use	2	1
Radiation therapy	3	0
Granulations	3	5
Prolapse	2	0
Leaking TEP	1	4
Aspiration of prosthesis	1	2

TEP — tracheoesophageal puncture.

eight of 21 (38%) neurectomized patients. Further, when both procedures were applied to achieve an enhanced result, five of 17 (29%) failed. This brought the overall failure rate secondary to resistance problems to 26 of 128, or 20% of the group.

The development of postoperative pharyngocutaneous fistulas delays recovery, eliminates oral intake, alters the effective scheduling of radiotherapy, prevents voice acquisition, promotes stricture formation, and may lead to carotid artery hemorrhage. In this series 20 patients (22%) who received no radiotherapy fistulized, and ten (26%) fistulized after radiotherapy exposure. Postoperative fistula formation occurred with total laryngectomy alone in 13% of the cases over the 9-year study period in both groups. Patients reconstructed with pectoralis major flaps had a fistula incidence of 20% in the earlier group, increasing to 75% in the later group.

There were four (5%) significant pharyngeal strictures in the later group that required secondary reconstruction; one previously irradiated patient developed progressive pharyngocutaneous necrosis that eventuated in a carotid blowout. In the earlier group, two patients developed esophageal prolapse through the TEP, with mechanical interference with prosthesis use.

Table 3 presents a group of puncture or prosthesis problems that include closure, extrusion, or inflammation. The incidence is relatively low, with improvement over time of maintenance of a patent TEP and a reduced incidence of tracheostomal stenosis. Dilatation and leakage of the TEP is present in 4% to 5% of cases and may require muscle flap reconstruction of the tracheoesophageal common wall.[12]

DISCUSSION

Primary restoration of voice after laryngectomy is an approach to laryngectomy rehabilitation that is parallel to the evolution of our experience with TEP and silicone voice prostheses. The methods and results have been presented above and span a 9-year period of clinical observations. The impetus for applying the voice prosthesis and puncture in the primary procedure is twofold. The findings from secondary experience demonstrated the reliability of the prosthesis and the durability of use in the TEP. The high quality of speech and high acquisition rate after laryngectomy presented a cogent argument for its application to the laryngectomy procedure itself. Finally, there have been a variety of procedures suggested by laryngologists over the last 100 years and summarized recently by Cantrell.[13] He stated that the fact that "none of these procedures became widely used indicated that problems existed with each. They were too complicated; they resulted in immediate complications such as unwanted fistulas and aspiration." It seemed reasonable to try to improve the status of shunt methods of voice restoration by the primary application.

The results of disease control discussed above are satisfactory in comparison to those of conventional laryngectomy series. There is no alteration of the basic laryngectomy operation or temptation to "shave resection margins dangerously close" or to practice "oncologic brinksmanship."[14] The additions to the total laryngectomy include a useful method for tracheostoma construction, improved TEP placement, and better pharyngeal wall relaxation. These simply are added to the operation with little additional time or experience.

The high rate of voice acquisition and quality is documented by the accumulating body of data.[15-17] Although prosthetic speech is an alternative to traditional esophageal speech methods, it exceeds this approach in intelligibility and acoustic characteristics.[18,19] Our experience suggests imperfect results when failures are considered in analysis of the results of the pharyngeal relaxation procedures, myotomy, or neurectomy. The failure rate has continued to drop with improved understanding of the surgical anatomy of the region and refinement of the operative techniques. Also, the secondary salvage of primary speech failures yields an improving success rate.

The morbidity and TEP complications are low in this series, whereas others feel that they are higher in frequency than this report mentions, and are a reason to defer the voice restoration procedure until healing is complete.[4,13] On the contrary, we feel that the treatment of laryngeal cancer currently demands immediate or primary reconstruction for voice production. The complications are few and are manageable. The delay in rehabilitation if the speech restoration is deferred is 3 to 6 months, and may lead to dependence, isolation, and depression. This no longer need be the case in the contemporary treatment of laryngeal cancer.

Primary voice restoration represents a compromise to the necessity for safe deglutition and an airway permanently separated from the digestive tract. As the voice prosthesis is a link from the trachea to the esophagus, the concept of TEP and prosthesis is a bridge to improved procedures in the future. The conservation laryngectomy procedures hold promise, but the near-total laryngectomy commits the patient to a permanent tracheostoma, which is a questionable advance. A significant improvement in the evolution of the laryngectomy procedure is the reconstruction of the upper airway. Adherence to accepted oncologic procedures and improved understanding of alaryngeal voice production may point the way.

REFERENCES

1. Singer MI. Tracheoesophageal speech: vocal rehabilitation after total laryngectomy. Laryngoscope 1983;93:1454-65.

2. Singer MI, Blom ED. An endoscopic technique for restoration of voice after laryngectomy. Ann Otol Rhinol Laryngol 1980; 89:529-33.

3. Johns ME, Myers EM. Speech rehabilitation following laryngectomy workshop [Editorial]. Head Neck Surg 1988;10: s87-9.

4. Ward PH, Andrews JC, Mickel RA, Hanson DG. Complications of medical and surgical approaches to voice restoration after total laryngectomy. Head Neck Surg 1988;10:s124-8.

5. Pearson BW. Subtotal laryngectomy. Laryngoscope 1981; 91:1904-11.

6. Staffierri M. La chirurgia riabilitativa della voce dope laringectomia totale. Bologna, Italy: Associazione Otologi Ospedalieri Italiani XXIX Congresso Nationale, 1976;5:222.

7. Singer MI, Blom ED, Hamaker RC. Further experience with voice restoration after total laryngectomy. Ann Otol Rhinol Laryngol 1981;90:498-502.

8. Hamaker RC, Singer MI, Blom ED, Daniels HA. Primary voice restoration and laryngectomy. Arch Otolaryngol 1985;11: 182-6.

9. Singer MI, Blom ED. A selective myotomy for voice restoration after total laryngectomy. Arch Otolaryngol 1981;107: 670-3.

10. Singer MI, Blom ED, Hamaker RC. Pharyngeal plexus neurectomy for alaryngeal speech rehabilitation. Laryngoscope 1986;96:50-3.

11. Singer MI, Hamaker RC, Blom ED. Voice restoration after total laryngectomy. In: Suen JY, Myers EM, eds. Cancer of the head and neck. 2nd ed. New York: Churchill Livingstone, 1989:593-620.

12. Singer MI, Hamaker RC, Blom ED. Revision procedure for the tracheoesophageal puncture. Laryngoscope 1989;99:761-3.

13. Cantrell RW. The case against immediate neoglottic reconstruction. Head Neck Surg 1988;10:s135-7.

14. DeSanto LW, Pearson BW, Olsen KD. Utility of near-total laryngectomy for supraglottic, pharyngeal, base-of-tongue, and other cancers. Ann Otol Rhinol Laryngol 1989;98:2-7.

15. Trudeau MD, Schuller DE, Hall DA. Timing of tracheoesophageal puncture for voice restoration: primary vs secondary. Head Neck Surg 1988;10:s130-4.

16. Stiernberg CM, Bailey BJ, Calhoun KH, Perez DG. Primary tracheoesophageal fistula procedure for voice restoration: the University of Texas Medical Branch experience. Laryngoscope 1987;97:820-4.

17. Blom ED, Singer MI, Hamaker RC. A prospective study of tracheoesophageal speech. Arch Otolaryngol 1986;112:440-7.

18. Robbins J, Fisher HB, Blom ED, Singer MI. A comparative acoustic study of normal, esophageal and TEP speech production. J Speech Hear Disord 1984;49:202-10.

19. Williams SE, Watson JB. Speaking proficiency variations according to method of alaryngeal voicing. Laryngoscope 1987; 97:737-9.

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XX INTERNATIONAL CONGRESS OF AUDIOLOGY

The XX International Congress of Audiology will be held October 14-18, 1990, in Tenerife, Canary Islands, Spain. For further information, contact Dr Jose Barajas, Presidente, C/Perez de Rozas, 8, 38004 Santa Cruz de Tenerife, Canary Islands, Spain; telephone 22 27 54 88; telex 91106.

Ann Otol Rhinol Laryngol 98:1989

SLIDING FLAP TRACHEOPLASTY

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The optimal method for surgical management of subglottic stenosis is based upon careful assessment of the location, caliber, length, and maturity of the stenotic segment, as well as associated conditions. For patients with a mature stenosis of short length, excision of the anterior arch of the cricoid and first ring and immediate reconstruction by means of a sliding flap of the next two to three rings of trachea offer a one-stage definitive treatment without the need for grafting. We report four cases of subglottic stenosis and one case of cricoid chondroblastoma in which reconstruction of the airway was successful and prompt. For carefully selected cases, sliding flap tracheoplasty may be a useful alternative to procedures in which the airway is expanded by means of grafting.

KEY WORDS — immediate reconstruction, subglottic stenosis, surgical excision.

INTRODUCTION

The most common lesion of the cricoid cartilage is subglottic stenosis, which may be congenital or acquired; neoplasm is rare. Subglottic stenosis requires treatment in proportion to the degree of airway narrowing and subsequent dyspnea. Key determinants in selecting therapy are the location, caliber, and length of the stenotic segment. Although mild degrees of airway narrowing may be tolerated, the work of breathing associated with even moderate stenosis usually necessitates intervention. In severe cases the threat to life mandates an emergent airway bypass procedure, most often tracheostomy.

Operative treatment of subglottic stenosis may require both endoscopic and external procedures. Endoscopic surgery includes dilation, injection of corticosteroid, removal of granulation tissue by forceps or laser, and a variety of laser techniques for removal of scar. External procedures are of two general types: airway expansion, and excision of the stenotic segment. Airway expansion has been the technique of choice in the subglottic region because of the unique anatomy of the posterior cricoid plate and the close relationship of the recurrent laryngeal nerves. However, we have applied the concept of subtotal excision, plus flap reconstruction, to carefully selected subglottic lesions and have found it to be a useful technique.

The purpose of this paper is to describe this approach and discuss our perspective regarding its role in the management of subglottic stenosis and other lesions of the cricoid cartilage.

METHODS

Case Selection. To be eligible for this procedure, the patient with stenosis must have a mature, uninfected subglottic cicatrix of short length (cricoid–first ring only) with a posterior lumen, an uninvolved segment between the vocal fold and the upper margin of the stenosis, and mobile vocal folds. Direct laryngoscopy must be performed to confirm these conditions. Patients with neoplasm confined to the anterior cricoid arch are also candidates for this procedure. The pertinent clinical details of the patients reported in this study are summarized in Table 1.

Surgical Technique. The neck is entered through a horizontal incision at the level of the cricoid cartilage, and the trachea and larynx are exposed in the midline. The thyroid isthmus is divided (if not already done), and the soft tissues are reflected laterally off the cricoid cartilage and upper tracheal rings. The cricothyroid membrane is divided horizontally to expose the upper margin of the stenosis and to confirm the absence of scar in the undersurface of the vocal folds. The inferior margin of the stenosis is determined by incremental sectioning of the trachea until a lumen of adequate size is reached. Then vertical incisions are made in the lateral wall of the trachea at the junction of the anterior two thirds and posterior third (Fig 1). The stenotic segment then is removed, and the vertical incisions are carried inferiorly for two to three rings to create an anterior tracheal flap. This is mobilized and slid upward to close the defect. Flexion of the neck helps, but a tension-free closure depends primarily on the adequate length of the flap and local mobility.

TABLE 1. DESCRIPTION OF PATIENTS

Patient	*Age*	*Sex*	*Year of Operation*	*Disorder*
1	60 yr	M	1972	Chondroblastoma of cricoid
2	4 mo	F	1986	Congenital subglottic stenosis
3	44 yr	F	1986	Acquired subglottic stenosis
4	38 yr	F	1987	Acquired subglottic stenosis
5	14 yr	F	1988	Acquired subglottic stenosis

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Presented at the meeting of the American Laryngological Association, San Francisco, April 1-2, 1989.

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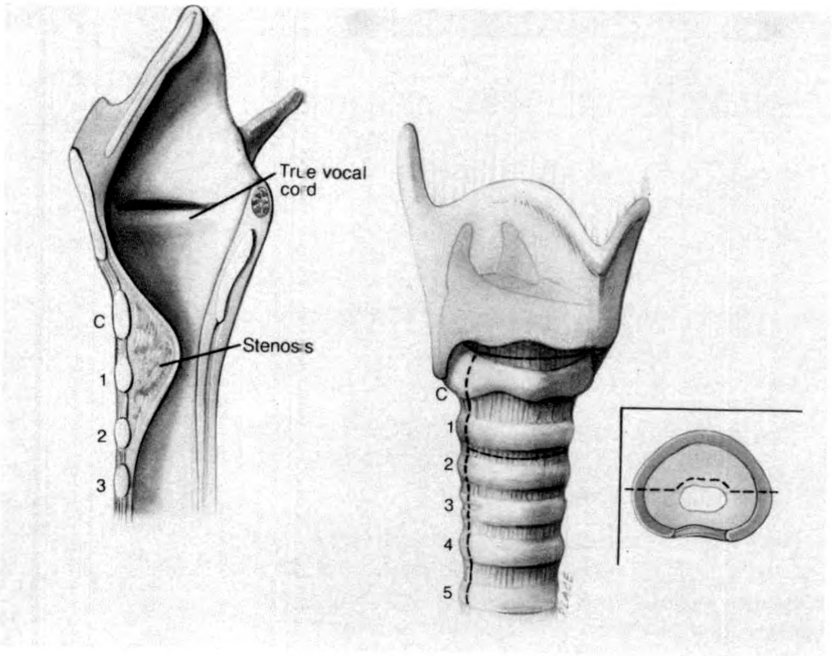

Fig 1. Usual location and extent of subglottic stenosis amenable to correction by sliding flap tracheoplasty. Note location of incisions outlined by dashed line. Care must be taken to preserve as much mucosa as possible, as depicted in small inset.

An Aboulker Teflon stent of the appropriate size is cut to length and placed such that the upper margin is just below the vocal folds and the lower margin is well below the stenotic segment but above the tracheostomy site. The stent is secured with a 2-0 nonabsorbable suture passed through strap muscles, trachea, and stent on each side and tied at the end of the procedure in the midline in the subcutaneous layer.

The flap is secured with five to seven interrupted absorbable sutures (3-0 Vicryl) placed between the upper margin of the flap and the lower border of the thyroid cartilage (Fig 2). Additional sutures may be used laterally to close the vertical incisions on each side, but generally only one stitch can be placed easily. Care is taken to place the sutures extraluminally. A cuffed tracheostomy tube is inserted to protect the incision line from increased air pressure (from coughing) and from secretions. The patient may resume a normal diet when pain permits. A nasogastric tube has not been used.

Postoperatively the patient receives the same antibiotic agent that was given at the start of the procedure until the stent is removed. Intensive care unit-level of care and monitoring is recommended. If wound healing is progressing satisfactorily, the stent is removed endoscopically after the seventh postoperative day and the patient is reexamined en-

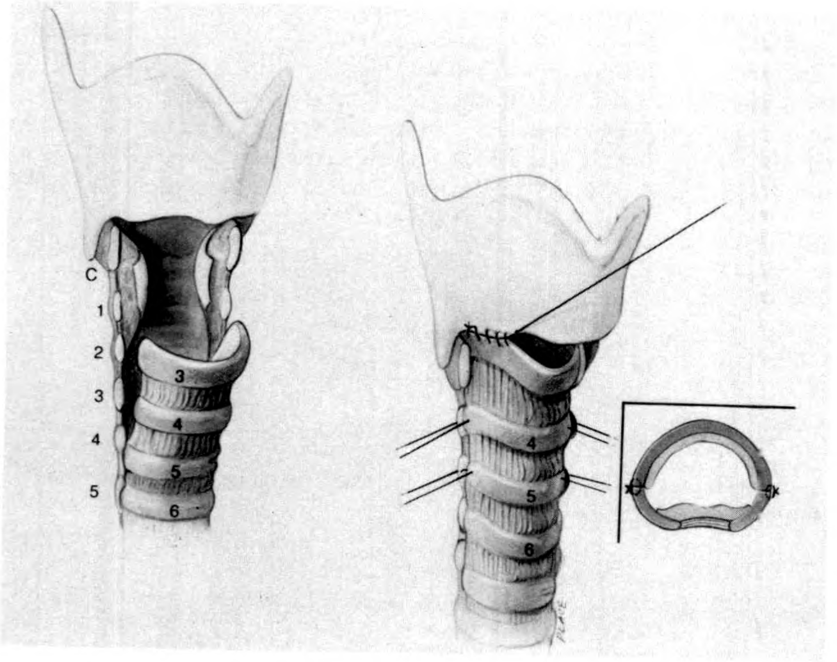

Fig 2. After resection of stenotic anterior two thirds of cricoid arch, small mucosal flaps are reflected laterally, and flap is advanced superiorly. Sutures should be absorbable and placed extraluminally to avoid granuloma formation. Not depicted is placement of Teflon stent (Aboulker) to stabilize suture line.

TABLE 2. PATIENT OUTCOMES

Patient	*Time of Stent Placement*	*Time of Decannulation*	*Other Treatment*
1	None	14 d	Laryngectomy at 5 yr
2	None	21 d	None
3	11 d	14 d	Two steroid injections
4	9 d	10 d	One steroid injection
5	9 d	14 d	None

doscopically 1 week later to assure the absence of infection and granulation tissue.

RESULTS

The procedure has been applied to one infant, one teenager, and three adults. Table 2 summarizes their subsequent clinical course.

All patients were extubated promptly. None have required repeat tracheostomy, and all have an airway that permits normal activity. Patients 3 and 4 both received endoscopic injection of triamcinolone acetonide into a small horizontal subglottic band to reduce what appeared to be a developing hypertrophic scar. Patient 1 underwent total laryngectomy 5 years later because of recurrence of the cricoid chondroblastoma.

DISCUSSION

Patients with subglottic stenosis of moderate degree and above require correction because of the risk of sudden death associated with prolonged tracheostomy.[1,2] The surgical management of subglottic stenosis poses unique challenges. In other anatomic sites a stenotic lesion is excised and either grafted or repaired primarily. Total excision of the cricoid is not feasible, because the posterior cricoid plate is a vital part of the laryngeal skeleton. In addition, its proximity to the vocal folds and recurrent laryngeal nerves endangers their function.[3] Allografts in the airway have not proven successful because of the problems of infection and tissue tolerance. Therefore, most surgical approaches to subglottic stenosis are based on the principle of expansion of the airway lumen by excision of intraluminal scar,[4] insertion of a homograft,[5] or both.[6]

Scar excision generally results in additional mucosal loss, and the resultant airway size depends upon the physiologic relining race between mucosal regeneration on the one hand and redeposition of scar on the other. Scar formation will dominate unless specific steps are taken to impede it, ie, injection of corticosteroid, stenting, or mucosal grafting (the latter has been uniformly unsuccessful). All of these steps require additional time and procedures.

Expansion of the airway through the interposition of a costal cartilage graft into a midline split of the cricoid cartilage and upper trachea has become the most widely used technique for lumen expansion.[4] In expert hands the decannulation rate is high. However, in our experience, the airway is seldom optimal (although most are quite adequate) because of persistent intraluminal scarring. In addition, technical failures from prolapse of the graft into the airway occur if extreme care is not taken to assure precise interposition.

For these reasons we sought a simpler technique that would minimize the amount of mucosal regeneration needed and avoid the need for a graft. The sliding flap technique relines the anterior two thirds of the subglottic space with normal tracheal epithelium supported by healthy cartilage. Only a small lateral remnant of excised scar is left to heal by mucosal regeneration. The Teflon stent provides a buttress for both the suture line and for the relining process.

The subglottic airway appeared perfectly normal in the two children (patients 2 and 5); a narrow horizontal scar band appeared in patients 3 and 4 at the upper suture line. Because both of these patients had developed stenosis secondary to hypertrophic scar formation after intubation, each received one or two injections of triamcinolone acetonide intralesionally for prophylaxis against additional hypertrophy; the scar bands subsequently thinned and did not re-form.

Indications and Limitations. This technique is clearly only applicable for circumscribed lesions of short length. The subglottic face of the vocal fold must be uninvolved, and the vertical length of the lesion must not extend below the first tracheal ring. Longer lesions would reduce the length of trachea available for relining and would require a longer flap to achieve closure. Given the limited blood supply of the trachea, we would be uncomfortable with a flap of longer than three rings.

The effect of the procedure on tracheal growth has not been studied. Given that the growth centers are based anterolaterally,[7] one would not expect difficulty. The infant in this series is now 3 years old and to date appears to be growing normally.

REFERENCES

1. Fearon B, Cotton R. Subglottic stenosis in infants and children: the clinical problem and experimental surgical correction. Can J Otolaryngol 1972;14:281-9.

2. Okamoto E, Fee WB, Boles R, Calcaterra TC, Dobie RA, Steadman MG. Safety of hospital vs. home care of infant tracheotomies. Trans Am Acad Ophthalmol Otolaryngol 1977;84:92-9.

3. Gerwat J, Bryce DP. The management of subglottic laryngeal stenosis by resection and direct anastomosis. Laryngoscope 1974;84:940-7.

4. Evans JNG, Todd GB. Laryngotracheoplasty. J Laryngol Otol 1974;88:589-97.

5. Cotton R. Management of subglottic stenosis in infancy and childhood. Review of a consecutive series of cases managed by surgical reconstruction. Ann Otol Rhinol Laryngol 1978;87:

649-57.

6. Aboulker P, Sterkers R, Demaldent E, Sauton P. Modifications apportées à l'intervention de Rethi. Ann Otolaryngol 1966; 83:98-106.

7. Tucker JA, Tucker GF. The development of the cricoid cartilage in staged human embryos and in fetuses. Presented at the meeting of the Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum, Munich, Sept 11, 1986.

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PAN AMERICAN ASSOCIATION OF OTORHINOLARYNGOLOGY-HEAD AND NECK SURGERY

The XXII Congress of the Pan American Association of Otorhinolaryngology-Head and Neck Surgery will be held November 23-27, 1990, in Catagena, Colombia. For further information, contact Pedro Blanco, President, Pan American Congress, Hospital Universitario del Valle, 3er Piso Servicio de Otorrinolaringologia, Cali, Colombia.

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INTERNATIONAL CONFERENCE AND WORKSHOP HEAD AND NECK CANCER REHABILITATION

An International Conference and Workshop on Head and Neck Cancer Rehabilitation will be held March 14-18, 1990, at the Ritz Carlton Hotel in Dearborn, Michigan. For further information, contact Department of Otolaryngology, Wayne State University, School of Medicine, 4201 St Antoine, 5E-UHC, Detroit, MI 48201; (313) 577-0804.

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CARBON DIOXIDE LASER POSTERIOR CORDECTOMY FOR TREATMENT OF BILATERAL VOCAL CORD PARALYSIS

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Upper airway obstruction due to bilateral vocal cord paralysis was successfully relieved by carbon dioxide laser posterior cordectomy. All patients achieved satisfactory airway and decannulation. Flow-volume loop spirograms obtained preoperatively and postoperatively documented improved flow rates on inspiration and expiration. Final voice quality was subjectively good in all patients. Follow-up has ranged from 1 year 10 months to 5 years 8 months, and initial improvement has been sustained in all cases. Carbon dioxide laser posterior partial cordectomy is an alternative management option for relief of upper airway obstruction due to bilateral vocal cord paralysis. The procedure can be performed without prophylactic tracheotomy. Subjectively good voice quality is preserved.

KEY WORDS — cordectomy, laser, vocal cord paralysis.

INTRODUCTION

The objectives in treatment of bilateral vocal cord abductor paralysis are to achieve 1) a safe and adequate airway, 2) preservation of voice quality, and 3) laryngeal competence. Historically, many different procedures have been proposed to improve the airway in bilateral vocal cord paralysis, including tracheotomy, cordectomy,[1] endoscopic[2] and external arytenoidectomy operations, vocal cord lateralization,[3-5] and vocal cord reinnervation procedures.[6] Presently, arytenoidectomy according to the technique of Woodman,[5] and carbon dioxide laser endoscopy[7] are probably most commonly practiced.

Tracheotomy was, and continues to be, a highly effective management of bilateral vocal cord paralysis. In 1922, Chevalier Jackson[1] proposed excision of the entire vocal cord and ventricle, but this produced a breathy voice. In 1932, Hoover[8] introduced submucous resection of the vocal cord, but scarring narrowed the glottis. In 1939, King[3] described an external approach of mobilization of the arytenoid cartilage and suture to the omohyoid muscle to activate the cord on inspiration. This operation was modified in 1941 by Kelly,[4] who removed the arytenoid through a window in the thyroid ala and lateralized the cord by suture. Woodman[5] in 1946 described arytenoidectomy using a posterolateral extralaryngeal approach and suturing the vocal process to the inferior cornu of the thyroid cartilage. This technique gained wide acceptance and remains the procedure of choice among many laryngologists. Endoscopic arytenoidectomy by electrocautery was introduced by Thornell[2] in 1948. Tucker[6] reported successful reinnervation of the posterior cricoarytenoid muscle utilizing an ansa hypoglossi nerve-muscle pedicle. This conceptually attractive operation may be useful in the freshly paralyzed larynx, but the long-term results have not met its original expectations. Since 1983, Ossoff et al[7,9] and others[10,11] have described endoscopic CO2 laser arytenoidectomy procedures. The long-term efficacy of this technique is awaited. Flow-volume loops have been studied to document the effects of surgical intervention after bilateral vocal cord paralysis.[12]

The foregoing procedures require tracheotomy, and airway obstruction is relieved at the expense of voice quality, which is breathy.

The CO2 laser endoscopic posterior partial cordectomy (PPC) operation described in this report has produced reliable improvement in the laryngeal airway, with a more satisfactory voice.

MATERIALS AND METHODS

Patients. Six women, 27 to 72 years of age, all with a history of thyroidectomy and bilateral vocal cord paralysis of 18 months' to 35 years' duration, underwent CO2 laser PPC and have been followed up from 1 year 10 months to 5 years 8 months (Table 1). All reported dyspnea on exertion, and all but one was dyspneic at rest. Three had subjectively "normal" voice, and three had weak but not hoarse voices. None reported subjective dysphagia (Table 2).

TABLE 1. PATIENT SUMMARY

Patient	*Age*	*Duration of BVCP*	*Tracheotomy*	*Time to Decannulation*
1	27	3 yr	Yes*	18 mo
2	36	18 mo	No	
3	40	25 yr	No	
4	53	29 yr	No	
5	56	13 yr	No	
6	72	35 yr	Yes	6 mo

BVCP — bilateral vocal cord paralysis.
*Presented with tracheotomy.

From the Department of Otolaryngology–Head and Neck Surgery, West Paces Ferry Hospital, Atlanta.

Presented at the meeting of the American Laryngological Association, San Francisco, April 1-2, 1989.

REPRINTS — Donald P. Dennis, MD, 3193 Howell Mill Rd, Suite 215, Atlanta, GA 30327.

TABLE 2. SYMPTOMS OF BILATERAL VOCAL CORD PARALYSIS

Pt	*Dyspnea at Rest*	*Dyspnea on Exertion*	*Swallowing Impairment*	*Cough While Eating or History of Pneumonia*	*Voice*
1	Yes	Yes	No	No	Normal
2	Yes	Yes	No	No	Weak
3	No	Yes	No	No	Normal
4	Yes	Yes	No	No	Normal
5	Yes	Yes	No	No	Weak
6	Yes	Yes	No	No	Weak

The operation is performed by suspension microlaryngoscopy under general anesthesia. The Dennis-modified (anterior Holinger-type, 10° angle) CO_2 laser Dedo laryngoscope was used to expose the posterior commissure (Fig 1). The Zeiss microscope using a 400-mm objective lens coupled to the CO_2 laser was used in all cases. The laser setting was 10 W with a 0.1-second repeat mode. Moistened neurosurgical pledgets were placed in the subglottic space to protect the trachea and endotracheal tube.

Surgical Procedure. A 3.5- to 4-mm C-shaped wedge of posterior vocal cord is excised from the free border of the membranous cord, extending 4 mm laterally. The excision begins anterior to the vocal process without exposing cartilage (Fig 2). This excision creates a 6- to 7-mm transverse opening at the posterior larynx (Fig 3A). The lased area is cleansed with moistened pledgets to remove char.

If the posterior airway opening is not adequate after 6 to 8 weeks, the excision is repeated or a smaller cordectomy is performed on the opposite side. This may produce a more breathy voice (Fig 3B).

Preoperative and Postoperative Care. All patients received 10 mg dexamethasone sodium phosphate (Decadron) and 1 g of cefazolin sodium preoperatively. Decadron was continued at 4 mg IV every 6 hours for 48 hours. Oral antibiotics were continued for 10 days. An aerosolized mist of 0.3 mL of racemic epinephrine in 3 mL of saline was given preoperatively and for 1 to 3 days postoperatively. The patients were observed overnight in an intensive care unit and were discharged in 2 to 3 days. Racemic epinephrine by an aerosolized mist Pulmonaid machine was used in two patients at home, and beclomethasone dipropionate (Beclovent oral inhaler) was used four times a day for 2 weeks postoperatively. A flow-volume loop spirogram was obtained preoperatively, and the examination was repeated after partial cordectomy. Forced inspiratory flow rate maximum was improved in all cases.

RESULTS

The clinical appearance of the larynx shows a white exudate for approximately 2 weeks, and final healing occurs by 4 to 8 weeks.

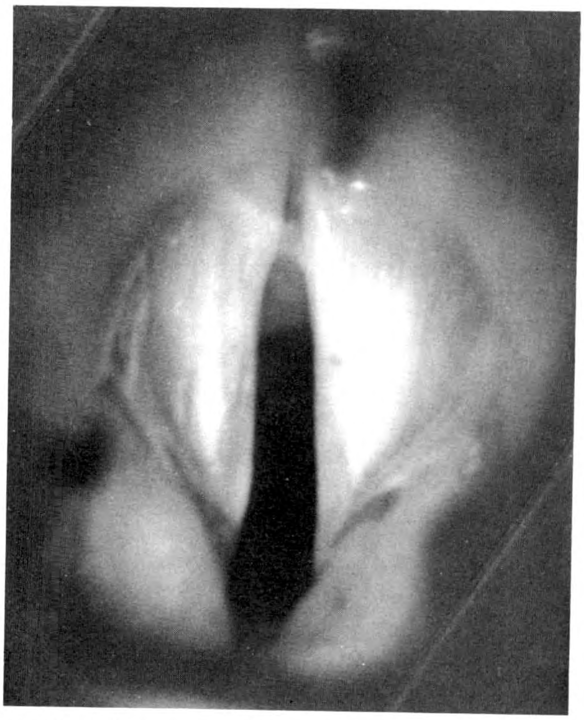

Fig 1. Endoscopic view of larynx with bilateral vocal cord paralysis. (Note: vocal cords are abducted halfway because of presence of laryngoscope.)

All patients had improvement of airway so that routine daily activities could be resumed without shortness of breath. One patient does daily aerobic exercises, and all others can climb four to five flights of stairs of five steps without dyspnea (Table 3). This subjective improvement was documented by comparing the postoperative flow-volume loop with the preoperative study (Table 4). In all six cases postoperative flow-volume loops showed improvement over preoperative values in forced inspiratory flow rate maximum and forced inspiratory flow rate at 50% (Table 4). The follow-up period was from 1 year 10 months to 5 years 8 months.

Voice quality continues to improve for 6 months to a year postoperatively. The final voice is subjectively good in that voice of adequate loudness and clarity is produced without undue effort.

There were no reports of swallowing impairment, cough-choke episodes, or aspiration.

Complications. The complications consisted of anterior web (patient 6) and the need for revision operations (patient 1 had three and patient 6 had two revision operations). Revision operations were necessitated by persistent vocal cord edema resulting in airway obstruction, and in one instance (patient 6) cord edema necessitated a temporary tracheotomy.

CASE REPORTS

Patient 1. A 27-year-old woman presented 11

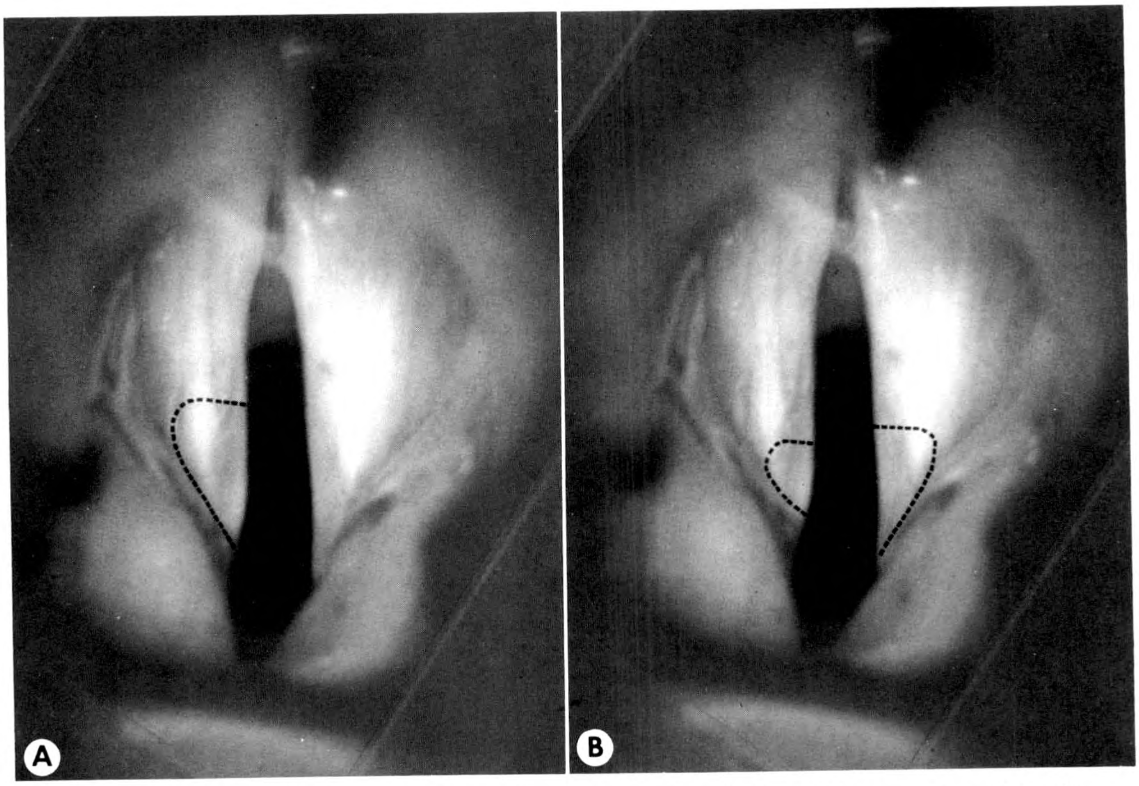

Fig 2. Views of larynx with dotted lines indicating lines of laser excision. A) Standard left posterior partial cordectomy. B) Standard right posterior partial cordectomy with lesser supplementary cordectomy on left.

months after failed reinnervation by bilateral ansa hypoglossi nerve-muscle pedicles.

This patient required three cordectomy procedures: the first operation was on the left vocal cord; 5 months later the left cord excision was repeated, together with a lesser right cord excision. Four months later a third left cord excision was done, and decannulation was achieved 9 months after the third operation. Presently she engages in daily aerobic exercises and enjoys subjectively good voice quality at 5 years 3 months of follow-up. This patient was the first patient in the series and depended upon her voice for her job; therefore, smaller cordectomies were done initially in order to preserve voice. The conservative excisions led to two revision operations necessary to achieve decannulation. In spite of the multiple excisions, her voice preservation has been good.

Case 6. A 72-year-old woman presented 35 years after thyroidectomy. Dyspnea was aggravated by coronary artery disease, mild congestive heart failure, and vocal cord edema due to allergy. She re-

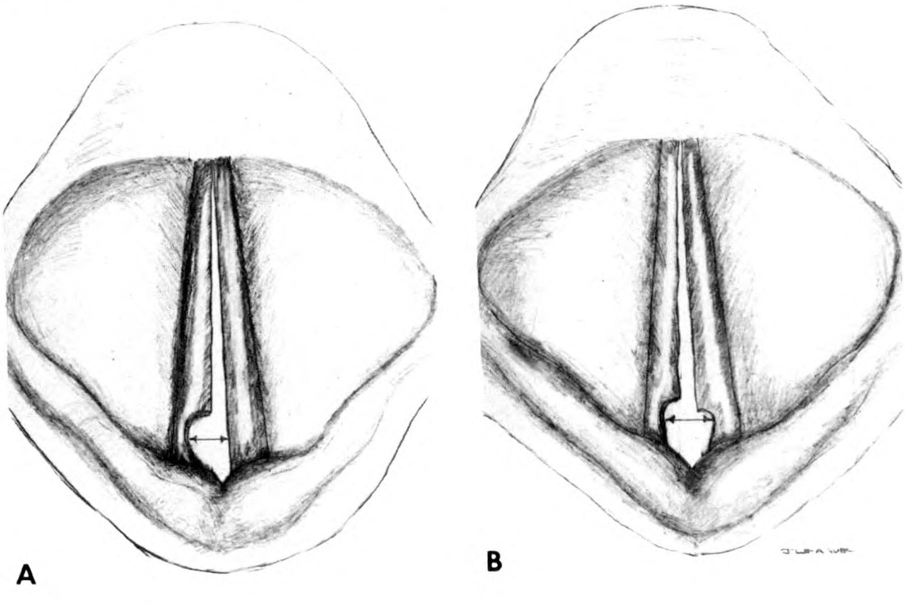

Fig 3. Diagrams of left posterior partial cordectomy. A) Showing 6- to 7-mm posterior laryngeal opening. B) With secondary smaller right posterior partial cordectomy to further widen posterior laryngeal airway.

TABLE 3. POSTOPERATIVE RESULTS

Patient	*Follow-up Period*	*Voice Quality*	*Exercise Tolerance*
1*	5 yr 3 mo	Good	Aerobics, 5 flights of stairs
2	5 yr 3 mo	Excellent	5 flights of stairs
3†	1 yr 10 mo	Good	5 flights of stairs
4†	2 yr 1 mo	Excellent	5 flights of stairs
5	5 yr 8 mo	Good	4 flights of stairs
6*	2 yr 10 mo	Good	Moderate walking§

*Had two or more laser cordectomies.

†Had bilateral cordectomies.

§Patient had significant coronary artery disease.

quired three laser procedures. The first was a bilateral PPC plus laser excision of obstructive polypoid edema of the anterior vocal cords. Three weeks later she developed anterior webbing and required a tracheotomy. Five weeks later she developed a second anterior synechia and had laryngeal dilation with bilateral revision cord excisions. One month later she redeveloped synechia and required CO2 laser lysis of adhesions, dilation, and endoscopic insertion of the Montgomery stent for 3 months. She was subsequently decannulated, and the stent was removed in 3 months with excellent results at 2 years 10 months of follow-up. This case underscores the importance of attaining optimum control of the inflammatory state and minimizing use of laser instrumentation.

DISCUSSION

The CO2 laser PPC evolved from the observation that patients having CO2 laser endoscopic excision of vocal process granulomas rarely experience voice change. It was reasoned that leaving the vocal process intact and creating a crescentic defect anterior to the vocal process would produce a 5- to 6-mm posterior airway opening and preserve a serviceable voice, since the anterior three fourths of the cord was preserved in position for good voice production.

Six patients underwent PPCs for treatment of bilateral vocal cord paralysis; all enjoyed airway improvement with preservation of subjectively good voice quality and no laryngeal incompetence.

The advantages of the procedure are simplicity in concept, reliability of outcome, no tracheotomy in most cases, low risk of complications, short hospitalization, adequate airway, good voice preservation, and suitability for revision operation when necessary.

Potential complications include granuloma and scar formation, postoperative edema necessitating tracheotomy, breathy voice quality, infection, arytenoid perichondritis (due to exposure of cartilage), and the known hazards that accompany CO2 laser use.

Any systemic or local disorder that predisposes to vocal cord edema increases the likelihood for tracheotomy. Manipulation of the anterior membranous cord with instruments should be avoided or minimized. Active inflammation and persistent polypoid change favor synechia and web formation. The presence of unresolvable anterior vocal cord edema is a relative contraindication to this procedure without tracheotomy.

The PPC is effective in relieving airway obstruction. Clinically, when an approximately 4- to 5-mm transverse posterior opening remains, sedentary daily activity can be performed without dyspnea. The cord excision defect remains open, because both ends of the lased muscle fibers contract to prevent closure. Granuloma formation has not been observed. The undisturbed anterior three fourths of the vocal cords are important for voice quality.

Indications for the PPC are bilateral vocal cord paralysis and airway obstruction severe enough that patients cannot perform their routine daily activities.

Relative contraindications to this procedure are persistent vocal cord edema and/or inflammation that cannot be resolved.

CONCLUSION

This is a retrospective analysis of six patients in whom CO2 laser PPC achieved upper airway enhancement without tracheotomy and maintained subjectively good voice quality.

TABLE 4. FLOW-VOLUME LOOP SPIROGRAM RESULTS

	Precordectomy						*Postcordectomy*				
Patient	*FVC (L)*	*FEFmax (L/s)*	*FEF50 (L/s)*	*FIFmax (L/s)*	*FIF50 (L/s)*	*Interval*	*FVC (L)*	*FEFmax (L/s)*	*FEF50 (L/s)*	*FIFmax (L/s)*	*FIF50 (L/s)*
1*	4.02	1.20	1.00	0.80	0.70	2 yr	3.61	2.09	1.04	1.48	0.61
2	4.26	4.00	3.48	1.22	0.78	5 yr	4.17	8.13	5.75	2.86	1.99
3†	3.33	5.10	4.22	1.25	0.84	1 yr 3 mo	3.28	6.66	5.30	2.00	1.20
4†	2.52	1.90	1.22	2.20	1.15	2 mo	2.99	3.77	3.30	2.94	2.22
5	2.90	3.40	1.60	1.40	1.36	1 mo	2.96	4.35	2.61	2.26	1.22
6*	2.55	4.29	3.40	1.02	0.55	2 yr 8 mo	2.62	6.23	4.95	2.58	2.40

FVC — forced vital capacity, FEFmax — forced expiratory flow rate maximum, FEF50 — forced expiratory flow rate at 50%, FIFmax — forced inspiratory flow rate maximum, FIF50 — forced inspiratory flow rate at 50%.

*Had two or more laser cordectomies.

†Had bilateral cordectomy.

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REFERENCES

1. Jackson C. Ventriculocordectomy, a new operation for the cure of goitrous glottic stenosis. Arch Surg 1922;4:257-74.

2. Thornell WC. Intralaryngeal approach for arytenoidectomy in bilateral abductor vocal cord paralysis. Arch Otolaryngol 1948;47:505-8.

3. King BT. A new and function restoring operation for bilateral abductor cord paralysis. JAMA 1939;112:814-23.

4. Kelly JD. Surgical treatment of bilateral paralysis of the abductor muscles. Arch Otolaryngol 1941;33:293-304.

5. Woodman D. A modification of the extralaryngeal approach to arytenoidectomy for bilateral abductor paralysis. Arch Otolaryngol 1946;43:63-5.

6. Tucker HM. Human laryngeal reinnervation. Laryngoscope 1976;86:769-99.

7. Ossoff RH. Endoscopic laser arytenoidectomy for vocal cord paralysis. Laryngoscope 1984;94:1293-7.

8. Hoover WB. Bilateral abductor paralysis, operative treatment of submucous resection of the vocal cord. Arch Otolaryngol 1932;15:337-55.

9. Ossoff RH, Karlan MS, Sissos GA. Endoscopic laser arytenoidectomy. Lasers Surg Med 1983;2:293-9.

10. Strong MS, Jako GJ, Vaughan CW, Healy GB, Polanyi T. The use of the CO2 laser in otolaryngology: a progress report. Trans Am Acad Ophthalmol Otolaryngol 1976;82:595-602.

11. Eskew JR, Bailey BJ. Laser arytenoidectomy for bilateral vocal cord paralysis. Otolaryngol Head Neck Surg 1983;91:294-8.

12. Cormier Y, Kashima HK, Summer W, et al. Upper airway obstruction with bilateral vocal cord paralysis. Chest 1979;75:423-7.

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PROSPECTIVE STUDIES EVALUATING THE STANDARD ENDOTRACHEAL TUBE AND A PROTOTYPE ENDOTRACHEAL TUBE

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Two prospective studies were designed to evaluate laryngeal injury sustained with the standard endotracheal tube (ETT) and the relative safety of a new prototype ETT. The first study followed patients after prolonged intubation with the standard ETT. Potential patient host factors were recorded and correlated with subjective complaints and objective findings on fiberoptic laryngoscopy. Nearly all patients sustained laryngeal injury after prolonged intubation, although over two thirds experienced resolution. Nasogastric feeding tubes and larger-diameter ETTs were associated with true vocal cord (TVC) granuloma formation. Duration of intubation was associated with delayed TVC immobility. The mechanisms of TVC granulomas and immobility are probably different, as suggested by the different host factor associations and onset times. The second study compared the standard ETT with the prototype ETT in short-term intubations. The prototype ETT was associated with no complications in this setting and is considered relatively safe for further testing in the patient with prolonged intubation.

KEY WORDS — endotracheal tube, intubation, laryngeal injury.

INTRODUCTION

Oral endotracheal intubation is an accepted alternative to tracheostomy for those patients requiring prolonged ventilatory support in many situations. This practice is based on the premise that prolonged oral endotracheal intubation is a relatively benign event with less morbidity than tracheotomy.[1-5] However, laryngotracheal injury after prolonged endotracheal intubation is a definite entity. Whited[1] documented a 14% incidence of laryngeal stenosis in patients intubated for more than 10 days. Kastanos et al[6] showed a 63% incidence of true vocal cord (TVC) ulceration and granuloma formation in critically ill patients intubated an average of 6.2 days. Stauffer et al[3] found a 19% incidence of tracheal stenosis after endotracheal intubation.

Postextubation and postmortem evaluations in larynges that have undergone prolonged intubation have shown clearly that the site of greatest and most frequent injury is in the posterior glottic structures. Specifically, the posterior commissure, cricoid cartilage, and vocal process of the arytenoid have been well documented as sites of mucosal and cartilaginous ulceration and/or granuloma formation.[3,7-10]

In a canine model evaluating the acute and chronic laryngeal changes after short- and long-term oral endotracheal intubation with the standard endotracheal tube (ETT), Weymuller[11] made the following observations. Laryngeal injury is related primarily to decreased mucosal perfusion in the areas of contact between the ETT and the posterior laryngeal structures. Fluorescein perfusion studies demonstrated that areas of contact with pressures exceeding capillary perfusion initiated ischemic injury within hours of intubation. Increased diameter of the ETT was related to higher lateral pressures and decreased mucosal perfusion within the posterior glottic structures. Direct laryngoscopy demonstrated the presence of injury at 2 weeks without subsequent improvement or deterioration of the injury. Duration of intubation was unrelated to the extent of laryngeal injury when evaluated by histopathology. It was concluded that "due to undefined host factors, the injury is variable in degree and not clearly related to the duration of intubation."[11]

These "undefined host factors" are poorly understood and not identified. They appear to be responsible for the wide spectrum of laryngeal injury seen in similar patient populations after prolonged oral ETT intubation. This question of host factors is addressed in the first part of the present work through a prospective study recording potential host variables and correlating them with postextubation subjective complaints and objective physical findings on direct laryngoscopy.

The second part of the present work evaluates a modified ETT designed to reduce the lateral pressure generated by the ETT against the posterior glottic mucosa.[11] The prototype ETT decreases the point pressure against the mucosa by distributing pressure over a greater surface area as a function of pressure = force/surface area.

The low pressure concept was implemented by construction of a foam-filled cuff (Fome-cuf, Bivona) around the ETT at the level of the TVCs. Com-

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TABLE 1. INJURY SEVERITY SCALE FOR ERYTHEMA AND ULCERATION

Erythema	0	No erythema, normal mucosa
	1	Mild erythema
	2	Moderate erythema of true vocal cords
	3	Severe erythema of true vocal cords only
	4	Severe erythema of true vocal cords and supraglottic structures
Ulceration	0	No ulceration, normal mucosa
	1	Ulceration of mucosa only, ≤3 mm in diameter
	2	Ulceration of mucosa only, >3 mm in diameter
	3	Ulceration of mucosa and arytenoid cartilage, ≤3 mm in diameter
	4	Ulceration of mucosa and arytenoid cartilage, >3 mm in diameter

paring the prototype ETT with the standard ETT in a canine model showed only the animals with the prototype ETT to have normal mucosal fluorescein perfusion in vivo and no laryngeal mucosal lesions on postmortem examination. Histologically, the mucosa had converted to a thickened stratified squamous epithelium with moderate chronic inflammation; however, mucosal granulation and ulceration were absent. The cartilage and cricoarytenoid joint were also normal.[11]

On the basis of these findings and after clearance by the Human Investigational Committee, we initiated an acute-phase prospective randomized patient-blinded study to evaluate the safety and efficacy of the prototype ETT in the setting of a short-term intubation.

METHODS

STANDARD ENDOTRACHEAL TUBE PROSPECTIVE STUDY

The effect of long-term oral intubation injury to the larynx with the standard oral ETT was evaluated in 42 patients at Harborview Medical Center over an 8-month period. The criteria for entry into the study were 1) that the patients be male and 18 years or older, 2) that they be without laryngeal or cervical spinal injury, and 3) that they had been orally intubated for 3 or more days. At the time of intubation patient age, patient diagnoses, and ETT size were recorded.

During intubation the patient was monitored daily for peak inspiratory pressure (PIP) and tracheal cuff pressure readings. Recorded were serum albumin levels, changes in Glasgow Coma Score (GCS) and Injury Severity Score (ISS), presence of a nasogastric feeding tube, number of reintubations, reason for the reintubation(s), conversion to a tracheostomy if performed, and cause of death if the patient died. The larynx was evaluated postmortem for injury with family consent.

After extubation the patients were evaluated for the presence of hoarseness (yes/no) and loss of voice power (yes/no). Laryngeal examinations were carried out at the bedside with a fiberoptic nasopharyngoscope after topical application of 2% viscous lidocaine. Patients were evaluated for presence of TVC erythema, ulceration, granuloma (yes/no, unilateral/bilateral), and immobility (yes/no, unilateral/bilateral). Erythema and ulceration were graded on a scale of injury severity from 0 to 4 (Table 1).

Consent for patient evaluation was obtained from the patient or the guardian. Patient laryngeal evaluations were discontinued after two examinations yielded normal results (defined by absence of erythema and ulceration) or if the patient was no longer available for follow-up. Forty-two patients were evaluated and placed into one of two groups: those who lived after extubation ($n = 33$) and those who died either during intubation ($n = 7$) or after extubation ($n = 2$; at 3 days and at 3 weeks). The larynges of deceased patients were evaluated postmortem for erythema, ulceration, and granuloma formation. In the live patient group, patient follow-up was continued at 7- to 14-day intervals until resolution of erythema and ulceration was documented. The average follow-up was 6.4 weeks until resolution ($n = 17$). The longest follow-up was 12 weeks. Those patients lost to complete follow-up (ie, resolution of laryngeal erythema and ulceration) were seen until 2.4 weeks ($n = 16$) after extubation. Results were analyzed by plotting dependent variables (hoarseness, loss of voice power, erythema, ulceration, granuloma formation, TVC immobility) against each other as well as against the independent variables (age, ETT size, diagnosis, duration of intubation, number of reintubations, tracheostomy, PIPs, serum albumin, GCS, ISS). Descriptive statistics as well as simple linear regression and X^2 comparisons were employed.

PROTOTYPE ENDOTRACHEAL TUBE PROSPECTIVE STUDY

The relative safety and efficacy of the prototype ETT were evaluated in a controlled patient-blinded prospective study in short-term elective intubations at Harborview Medical Center over a 3-month period. Forty-two patients were randomized into two equal groups. One group received the standard ETT, and the second group received the prototype ETT. Criteria for entry into the study were 1) that the patients be healthy, male, and 18 years or older, 2) that they be without laryngeal or cervical spine injuries, 3) that they had no recent prior intubations, and 4) that they have a low "anesthetic risk" (ASA of 1 or 2).

Anesthesiologists were asked to evaluate the standard or prototype ETT at the time of intubation for difficulty with oral intubation, successful passage of the suction catheter, volume of air required to in-

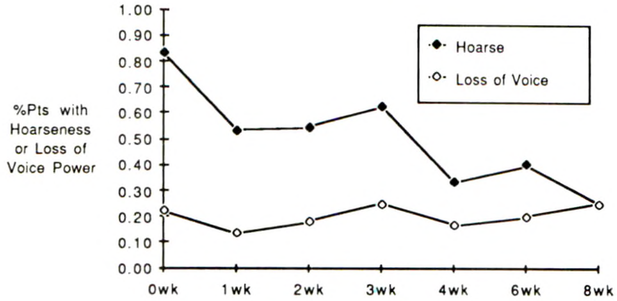

Fig 1. Percentage of live patient group (n = 18) with hoarseness and loss of voice power from time of extubation. Patients without resolution of hoarseness and/or loss of voice power had true vocal cord granuloma(s) and/or immobility.

flate the distal tracheal cuff to obtain a seal, difficulty with extubation, and evidence of laryngospasm. The patient was questioned on the day of intubation and the day following intubation for complaints of sore throat, cough, aspiration, stridor, or hoarseness. Results were quantified and compared by χ^2 analysis.

RESULTS

STANDARD ENDOTRACHEAL TUBE PROSPECTIVE STUDY

The average age of all 42 patients was 47 years (range, 21 to 85). The average age of the 33 patients from the live patient group was 45 years, and of the nine patients from the deceased group, 53 years. Size of ETTs ranged from No. 7 to No. 8.5. Fifty-two percent of all patients received a No. 8 tube, and 39% a No. 7.5 tube. The major diagnoses in the order of frequency were traumatic>>neurologic>vascular>medical (hypertensive episode, pneumonia, overdose). The causes of death were trauma in five patients, vascular disease in two patients, closed head injury in one patient, and overdose in one patient.

In the live patient group, the average duration of intubation was 9.8 days (SEM = 1.9; range, 3 to 54 days). Twenty-one patients (64%) were intubated from 3 to 7 days, five patients (15%) were intubated from 8 to 12 days, four patients (12%) were intubated from 13 to 17 days, and the remaining three patients were intubated from 33 to 54 days.

In the live patient group, 17 reintubations occurred in 11 patients. Reasons for reintubation included 12 self-extubations, four failed extubation attempts, and one controlled reintubation in the operating room. Twenty-one patients (64%) were not reintubated, nine (27%) were reintubated once, two (6%) were reintubated twice, and one (3%) was reintubated five times. Ten patients were converted to a tracheostomy (30%). The average PIP was 37 cm H_2O (SEM = 1.6). Tracheal cuff pressures were maintained constantly between 24 and 30 cm H_2O as dictated by respiratory therapy standard protocol. Serum albumin levels during intubation were 2.4 g/dL (SEM = 0.2; normal range, 3.5 to 5.2 g/dL). Only 10% of this group had normal albumin levels during intubation. Twenty-six patients (80%) had a nasogastric tube (NGT) while intubated, and 19 patients after extubation. The difference in average ISS and GCS improved from intubation to extubation by 1.6 and 2.6, respectively.

In the deceased group, the average duration of intubation was 8.2 days (SEM = 1.8). There were three reintubations in three patients, due to two failed extubation attempts and one self-extubation. One patient was converted to a tracheostomy. The average PIP was 39 cm H_2O (SEM = 3.3). The albumin levels during intubation averaged 3.2 g/dL (SEM = 0.8). All nine patients had NGTs. No significant change in ISS or GCS from intubation to extubation was demonstrated.

Signs and Symptoms of Laryngeal Injury. Occurrences of hoarseness and loss of voice power are shown in Fig 1. The presence of hoarseness was evaluable in 18 patients; the remainder could not be evaluated because of a tracheostomy tube or comatose state. Of these, 15 patients (83%) demonstrated hoarseness postextubation. Hoarseness resolved within 4 weeks, except in seven patients who also had TVC granuloma(s) (n = 4) and/or immobility (n = 5). Patients with hoarseness had an average PIP of 41 cm H_2O (SEM = 2.9), and patients without hoarseness had an average PIP of 34 cm H_2O (SEM = 1.5). Four patients (22%) demon-

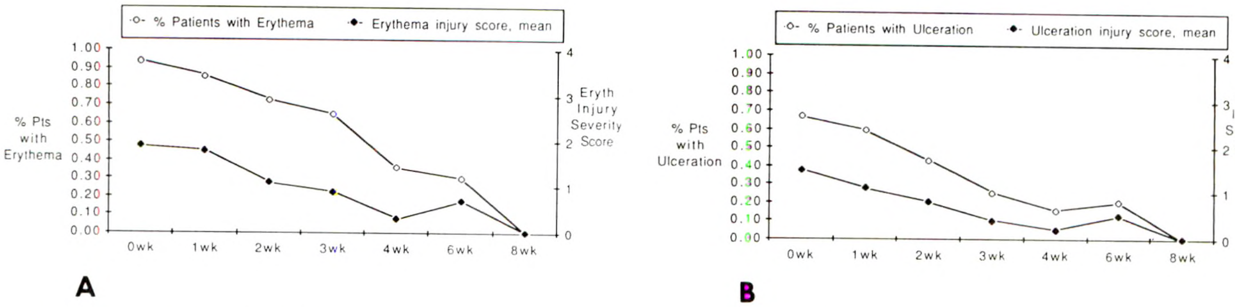

Fig 2. Percentage of patients from live patient group (n = 33) A) with erythema, and severity of their erythema over time, and B) with ulceration, and severity of their ulceration over time. Note that by 8 weeks all patients had resolution of erythema and ulceration.

TABLE 2. TRUE VOCAL CORD GRANULOMA(S) AND IMMOBILITY AND THEIR ASSOCIATIONS WITH HOST FACTORS (N = 33)

Injury	*No. of Patients*	*Bilateral Injury (No. of Patients)*	*Previous Erythema and/or Ulceration (No. of Patients)*	*Hoarseness and/or Loss of Voice Power (No. of Patients)*	*Prior Nasogastric Tube (No. of Patients)*	*Relative Risk of Endotracheal Tube No. 8 v No. 7.5*	*Mean Duration of Intubation (d)*	*Time of Onset After Extubation (wk)*
Granuloma	9	6	9	4*	9 (p = .09)	4 (p = .10)	13 (p = .52)	3.5
Delayed true vocal cord immobility	4	0	4	2†	4 (p = .34)	0.31 (p = .25)	18 (p = .04)	8.0

*Seven of nine patients with granuloma were evaluated for hoarseness and/or loss of voice power. Other two were comatose.

†Other two had tracheotomy.

strated persistent loss of voice power postextubation that lasted for the duration of the study. Of these, all four had TVC granuloma(s) and/or immobility. No cases of stridor were observed.

Numbers of cases of glottic erythema and ulceration are shown in Fig 2. In the live patient group, 31 of 33 patients (94%) demonstrated erythema of the glottis after extubation. Twenty-two patients (67%) demonstrated ulceration of the glottis after extubation. Erythema and/or ulceration was found consistently at the junction of the posterior one third and anterior two thirds of the TVC, in the region of the vocal process of the arytenoid cartilage. This epicenter of injury was constant. As the severity of the injury increased, deeper tissue and surrounding tissue became involved.

In the live patient group, the initial average erythema severity score was 1.9, representing moderate TVC erythema (SEM = 0.2; range, 0 to 4). The initial ulceration severity score averaged 1.5 (SEM = 0.3; range, 0 to 3), representing mucosal ulceration >3 mm in area without cartilage exposure. The presence and the severity of erythema and ulceration decreased in a near-linear fashion with time. At 8 weeks all patients had resolution of laryngeal erythema and ulceration, although some had subsequent granuloma formation or TVC immobility. Of those patients without documented resolution of injury and lost to follow-up, 16 had an average erythema severity score of 1.0 and an average ulceration severity score of 0.8 at an average of 2.4 weeks postextubation. These values are consistent with the time frame of injury resolution represented in Fig 2. Higher GCSs were correlated with a more rapid resolution of erythema (p = .02) and less erythema on initial examination (p = .04). Tracheostomy resulted in prolonged laryngeal erythema (p = .03) compared to that in patients without a tracheostomy. Duration of intubation and size of ETT did not correlate with the severity of erythema or ulceration present on the patients' first examination or with the duration of erythema and ulceration.

Table 2 shows occurrences of TVC granuloma formation. In the live patient group, nine of 33 patients (27%) developed granuloma(s) on the vocal process of the arytenoid. Six of the nine patients had bilateral granulomas. All patients had previous erythema and/or ulceration. Of the seven patients with granulomas who were evaluated for voice, four (57%) had hoarseness and/or loss of voice power. Granulomas were seen only in those patients with an NGT while intubated (p = .09). Patients were at an increased risk of granuloma formation if intubated with a No. 8 versus a No. 7.5 ETT (p = .10). Those patients in whom granulomas were identified were somewhat older as a group than those without granuloma formation: 59 years old (SEM = 7.4) versus 48 years old (SEM = 5.0). The development of granulomas was delayed, with the average time of onset at 3.5 weeks after extubation. Of the patients with granulomas, four had resolution of the granuloma, at an average of 8 weeks. Duration of oral endotracheal intubation, PIP, albumin, ISS, GCS, and presence of tracheostomy did not correlate with granuloma formation. No cases of posterior commissure webbing were observed.

Cases of TVC immobility are numbered in Table 2. Six cases (18%) of unilateral TVC immobility were observed in the 33 patients studied. Two were noted at extubation in patients suffering from a probable recurrent laryngeal nerve injury (gunshot wound and stab wounds to chest). The remaining four cases were delayed in onset, with documented normal TVC motion prior to the immobility. No cases of bilateral TVC immobility were observed. All patients had previous erythema and/or ulceration. Of those able to speak, both were hoarse and one had loss of voice power. Immobility of the TVCs was seen only in those patients with an NGT while intubated, but the number of patients evaluated was too small to approach significance (p = .34). No trend existed with size of ETT used (p = .25). However, the duration of oral endotracheal intubation significantly correlated with development of TVC immobility (p = .04). The average delay of onset of TVC immobility was 8 weeks. One of the four patients had resolution of the immobility at 12 weeks. Age, number of reintubations, PIP, albumin, ISS, GCS, and presence of tracheostomy did not correlate with TVC immobility.

Within the deceased group of patients, postmortem examination revealed an erythema injury severity score of 3.43 (SEM = 0.37) and an ulceration injury severity score of 2.86 (SEM = 0.63). These scores were significantly worse than those in the live patient group. No granulomas were identified in the deceased group, except for the patient surviving 3 weeks before dying.

PROTOTYPE ENDOTRACHEAL TUBE PROSPECTIVE STUDY

The average age and duration of intubation in each study group were 39 years old and 1.8 hours (standard ETT) and 31 years old and 3.0 hours (prototype ETT). The anesthesiologists found no significant difference between the standard ETT and the prototype ETT regarding intubation, passage of the suction catheter, volume of air to seal the distal tracheal cuff, or difficulty with extubation. One case of laryngospasm occurred in the 42 patients studied. The event occurred in a patient intubated with the prototype ETT and was managed without reintubation or complication. Patient-blinded evaluation of symptoms on the day of intubation and the day after intubation revealed no significant difference between the standard and prototype ETTs regarding sore throat, cough, aspiration, stridor, or hoarseness. No complications occurred in the study as a result of either ETT.

DISCUSSION

Laryngeal injury from prolonged intubation has been recognized for some time. Less well understood are the potential host factors associated with laryngeal injury. The ETT material, contact pressure as related to increasing ETT diameter, and duration of intubation all have been associated with laryngeal injury. The first section evaluated the standard ETT in prolonged oral intubation and identified possible host factors that correlate with certain types of laryngeal injury. The second section tested the relative safety and efficacy of the prototype ETT in an acute phase study.

STANDARD ENDOTRACHEAL TUBE PROSPECTIVE STUDY

Hoarseness occurred in a large percentage of patients during the postextubation period; however, all patients experienced resolution except for those with TVC granulomas(s) or immobility. The resolution of hoarseness in those patients without TVC granuloma(s) or immobility followed a similar time course as that seen with erythema and ulceration. Patients with hoarseness had a higher average PIP than those without hoarseness. The higher flow rates of air escaping through the glottis (ie, cuff leak) may be responsible in part for hoarseness through damage to the TVC epithelium. Loss of voice power occurred less often than hoarseness, tended not to resolve, and more frequently was associated with TVC immobility. Those patients without resolution of hoarseness at 7 weeks should be considered highly suspect for either TVC granuloma or immobility. Not all patients with granuloma formation had hoarseness, but both patients with TVC immobility manifested hoarseness and one had loss of voice power. Hoarseness and loss of voice power may be the only outward signs of postintubation laryngeal injury. In patients with a tracheostomy or with decreased mentation these symptoms are absent and a laryngeal injury is likely to go unrecognized.

The association of tracheostomy and prolonged erythema injury was significant; this observation is consistent with the work of Kirchner and Sasaki[4] suggesting that the presence of a foreign body and a tracheocutaneous conduit for bacteria would predispose to more inflammation within the glottis. Size of the ETT and duration of intubation did not correlate with injury severity. Erythema and/or ulceration were present in all patients developing TVC granulomas; however, the severity of erythema and ulceration did not consistently predict those who developed TVC granulomas or immobility.

Nasogastric intubation antedated all cases of TVC granuloma(s). This may be a function of increased gastroesophageal reflux resulting from compromise of the lower esophageal and cricopharyngeal sphincters. The acidic contents refluxing in the region of the glottis and ETT may be sufficient to promote granuloma formation in the presence of a foreign body. Sofferman and Hubbell[12] demonstrated a 30% incidence of arytenoid edema in patients intubated nasogastrically and not with an ETT. They proposed several potential pathophysiologic mechanisms, including frequent motion of the posterior cricoid mucosa against the NGT, fixed by the cricopharyngeus muscle. They also proposed that the NGT is compressed between the larynx and cervical spine when the patient is in a supine position, thereby decreasing local mucosal perfusion. Our study suggests that simultaneous use of the ETT and NGT appears to place the larynx at an even higher risk. The No. 8 ETTs were associated with more frequent granuloma formation than were the No. 7.5 ETTs. Suggested pathophysiology is seen in the canine model, with increasing ETT diameter and decreased mucosal perfusion documented by fluorescein studies.[11] Duration of intubation did not correlate with granuloma formation.

Immobility of the TVC resulting from oral ETT intubation also has been described by Whited,[2] who reported 16 patients with transient immobility after intubation for 5 days, the majority of whom returned to normal. He suggested that the mechanism was a function of mechanical trauma with resultant edema, ulceration, and inflammation of the larynx limiting normal motion. In addition, several of his patients suffered delayed laryngeal stenosis over a period of months.[1] In the present study no cases of acute or delayed stenosis were observed, but four cases of delayed TVC immobility were documented. We are unaware of any previous reports of delayed TVC immobility. In the canine model of prolonged intubation there was histologic evidence of inflammation and fibrovascular infiltration of the cricoarytenoid joint in those animals intubated with a standard oral ETT.[11] Our results suggest that delayed TVC immobility appears to have a different cause than granuloma formation, because the associated host factors are different. Specifically, duration of intubation was significantly related to TVC immobility, but the presence of an NGT and the size of the ETT were not. The reverse of this was true for TVC granuloma formation, ie, the presence of an NGT and the size of the ETT were associated with TVC granuloma formation, but duration of intubation was not. In addition, the time of delayed onset was also different (Table 2).

Possible pathophysiologic mechanisms to explain these findings can be drawn from the work of the above-referenced authors. Formation of TVC granuloma may result from ETT-induced decreased mucosal capillary perfusion with resultant inflammation and granulation tissue formation, exacerbated by gastroesophageal acid reflux and local friction from an NGT. Immobility of the TVCs may result from chronic stenting, with cricoarytenoid joint synovial inflammation and fixation. After the stent (ETT) is removed the local inflammatory response takes time to resolve. This resolution time may be even longer if other sources of inflammation are present. Cricoarytenoid joint inflammation may lead to ankylosis. Sofferman and Hubbell[12] reported that the presence of an NGT alone will lead occasionally (four cases) to TVC immobility. Although the association of TVC immobility with the presence of an NGT did not achieve statistical significance, all four patients with delayed TVC immobility had an NGT after extubation.

PROTOTYPE ENDOTRACHEAL TUBE PROSPECTIVE STUDY

The prototype ETT design is based on the premise that increasing the surface area of contact between the ETT and the posterior glottis decreases the point pressure to the laryngeal mucosa. Use of the prototype ETT in the canine model supports this concept.[11] Prior to testing the prototype ETT for prolonged intubation in the human, an acute phase study was undertaken in a healthy low risk population. The acute phase study compared the standard and prototype ETTs on the basis of the anesthesiologists' evaluation of the difficulty of use and the patients' evaluation of symptoms postintubation. In both groups of evaluators there were no significant differences between the standard and prototype ETTs. The canine model and the acute phase prototype ETT in our human study support the thesis that the prototype ETT is relatively safe and likely to decrease the laryngeal injury inherently associated with prolonged intubation. A prospective randomized study comparing the standard and prototype ETTs in patients intubated for prolonged intervals is in progress.

CONCLUSION

A prospective study evaluating laryngeal injury in patients experiencing prolonged oral endotracheal intubation with the standard ETT revealed several host factors associated with specific and different laryngeal injuries. A second prospective study of the prototype ETT with a Fome-cuf at the level of the TVCs supports its relative safety and efficacy in short-term oral intubations. A chronic prospective study evaluating the prototype ETT for prolonged endotracheal intubation is presently under way.

REFERENCES

1. Whited RE. A prospective study of laryngotracheal sequelae in long-term intubation. Laryngoscope 1984;94:367-77.

2. Whited RE. Laryngeal dysfunction following prolonged intubation. Ann Otol Rhinol Laryngol 1979;88:474-8.

3. Stauffer JL, Olson DE, Petty TL. Complications and consequences of endotracheal intubation and tracheotomy. Am J Med 1981;70:65-76.

4. Kirchner JA, Sasaki CT. Fusion of the vocal cords following intubation and tracheostomy. Trans Am Acad Ophthalmol Otolaryngol 1973;77:88-91.

5. Deane RS, Mills EL. Prolonged nasotracheal intubation in adults: a successor and adjunct to tracheostomy. Anesth Analg 1970;49:89-97.

6. Kastanos N, Miro RE, Perez AM, Mir AX, Agus TI, Vidal A. Laryngotracheal injury due to endotracheal intubation: incidence, evolution, and predisposing factors. A prospective long-term study. Crit Care Med 1983;11:362-7.

7. Bergstrom J, Moberg A, Orell SR. On the pathogenesis of laryngeal injuries following prolonged intubation. Acta Otolaryngol (Stockh) 1962;55:342-6.

8. Donnelly WH. Histopathology of endotracheal intubation: an autopsy study of 99 cases. Arch Pathol 1969;88:511-20.

9. Hilding AC. Laryngotracheal damage during intratracheal anesthesia. Demonstration by staining the unfixed specimen with methylene blue. Ann Otol Rhinol Laryngol 1971;80:565-81.

10. Lindholm C-E. Prolonged endotracheal intubation. Acta Anaesthesiol Scand [Suppl] 1969(suppl 33).

11. Weymuller EA Jr. Laryngeal injury from prolonged endotracheal intubation. Laryngoscope 1988;98(suppl 45).

12. Sofferman RA, Hubbell RN. Laryngeal complications of nasogastric tubes. Ann Otol Rhinol Laryngol 1981;90:465-8.

Ann Otol Rhinol Laryngol 98:1989

AUDITORY BRAIN STEM RESPONSES TO BONE-CONDUCTED TONES IN INFANTS

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The auditory brain stem responses (ABRs) to 500- and 2,000-Hz bone-conducted (BC) tones were recorded from 48 infants with ears exhibiting various external and middle ear states (normal, otitis media, auditory meatal atresia). Amplitudes were greater, wave V latencies longer, and detectability better for responses to 500-Hz BC tones compared to 2,000-Hz BC tones. Overall, most (94% to 100%) infants with normal cochlear sensitivity demonstrate ABRs to 20-dB normal hearing level (nHL) 500-Hz BC tones and 30-dB nHL 2,000-Hz BC tones. In cases in which masking is difficult (eg, bilateral atresia), infant ipsilateral/contralateral ABR asymmetries may help determine from which cochlea a response to the BC tones originates. In conclusion, two-channel ABR recordings to BC tones appear to be feasible for demonstrating normal cochlear sensitivity in infants.

KEY WORDS — auditory brain stem response, aural atresia, bone conduction, conductive impairment, infant, response asymmetry.

INTRODUCTION

The primary goal of evoked potential audiometry is to provide the same audiometric information for infants and difficult-to-test children as is routinely provided by pure tone behavioral audiometry for older patients. This information includes thresholds at specific frequencies for both air-conducted and bone-conducted (BC) stimuli.

The auditory brain stem response (ABR) to air-conducted clicks is the most widely employed evoked potential audiometry technique. While informative and accurate in most cases, the use of clicks has many drawbacks.[1-4] Clicks cannot provide information concerning sensitivity for specific frequencies; ABR thresholds for clicks usually underestimate low frequency sensitivity. Further, the use of clicks has been demonstrated to miss significant impairments restricted to low, middle, or high frequency regions.[4-7] In contrast, several studies have demonstrated the satisfactory accuracy of the ABR to short duration tones for estimating pure tone behavioral thresholds.[3,5,6,8-11] These tone-ABR recordings, however, are more demanding technically and require careful attention to stimulus (eg, tone rise time), recording (eg, electroencephalographic [EEG] filter bandpass, analysis time), and response interpretation considerations.[4,12]

Several studies have investigated the brain stem responses to BC clicks, with most demonstrating the feasibility of the technique for estimating cochlear sensitivity.[13-17] The acoustic spectrum of a click transduced through a bone oscillator, however, is significantly different from that of an air-conducted click.[14-18] Thus, comparisons between air-conducted and BC click results may not always be valid. As with air-conducted clicks, ABR results obtained with BC clicks are limited in that no information is provided regarding specific frequencies.

Little information exists about ABR to BC tonal stimuli.[19] A recent study of the effects of ipsilateral high-pass noise masking indicates that the frequency specificity of normal-hearing adults' ABRs to 500- and 2,000-Hz BC tones is similar to that of their air-conducted results, although with somewhat better frequency specificity for the 500-Hz BC stimuli.[20] No reports have been published concerning these responses in infants.

Impairment of middle ear conduction, such as that caused by otitis media (OM), is a common condition during infancy. Estimates of cochlear sensitivity are required for these infants, as well as for infants with external auditory meatal atresia and other cranial-facial malformations. Although difficult to obtain, this information is important for subsequent decisions concerning these patients' management, including surgery. Such information might be obtained by recording the ABR to BC tones.

The present study is a preliminary investigation of the ABR to 500- and 2,000-Hz BC tones recorded from a diverse group of infants. Infants with ears exhibiting a wide range of external and middle ear status (normal, OM, atresia) were tested in order to assess this technique's ability to demonstrate normal cochlear sensitivity in the infant population. No infants with sensorineural impairment, however, were tested, and possible differences between results from normal ears and those from ears with OM or atresia were not investigated. This study also investigated whether two-channel (ipsilateral/contralateral) ABR recordings provide additional information concerning the laterality of response origin.

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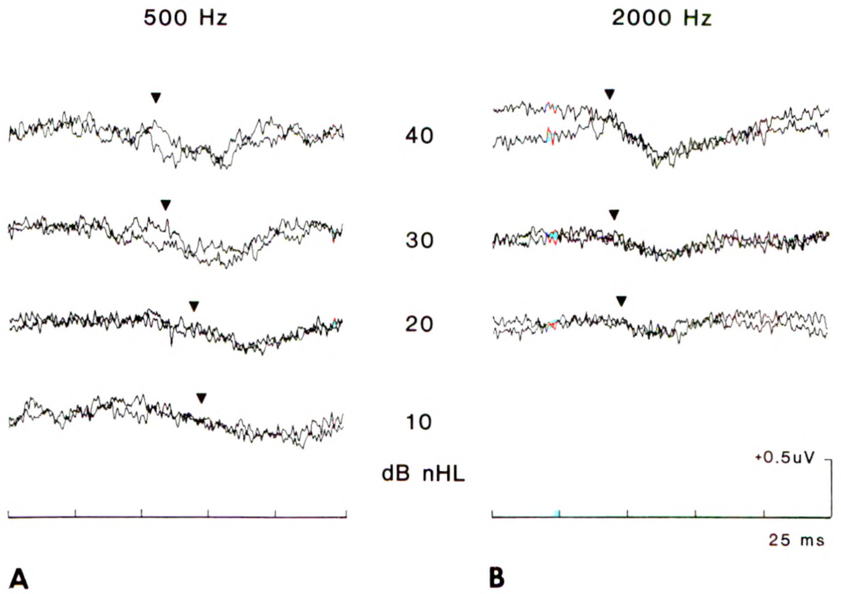

Fig 1. Brain stem responses recorded from 4-month-old infant with normal middle ear status. Response presence determined from replicability of any component following stimulus offset (500 Hz, 10 ms; 2,000 Hz, 3 ms). Contralateral ear was not masked. Arrows — approximate wave V latency. A) 500-Hz bone-conducted tones. B) 2,000-Hz bone-conducted tones.

MATERIALS AND METHODS

A total of 48 infants participated in this study. All infants were between 2 weeks and 2 years of age (mean age, 6.1 months; standard deviation, 3.6 months) at the time of testing. Infants were excluded from this study if they failed to demonstrate ABRs to 80-dB nHL air-conducted clicks (n = 1) or demonstrated ABR wave I to wave V interpeak latency prolongations (n = 3).

Eleven of the 48 infants who participated were referred for behavioral audiologic and ABR evaluations because of a diagnosis of unilateral (n = 6) or bilateral (n = 5) external auditory meatal atresia. The possibility of mild sensorineural hearing loss in atretic ears could not be ruled out firmly; however, computed tomographic scans from these 11 infants suggested normal development of inner ear structures. Their atretic ear ABR thresholds for air-conducted clicks were 60 to 80 dB nHL with substantially prolonged latencies. Same-day or follow-up behavioral audiologic testing (n = 6) indicated normal sensitivity to nonmasked BC pure tones in at least the better ear.

Twenty-eight of the remaining 37 infants are being followed up by the Low Birthweight Infant Follow-up and Evaluation (LIFE) program of the Albert Einstein College of Medicine and have demonstrated normal ABR thresholds to air-conducted clicks and tones and normal behavioral audiologic results. The remaining nine infants were referred for clinical ABR testing because of perinatal history and/or parental concern. Of these nine infants, one subsequently demonstrated normal behavioral audiologic thresholds, six demonstrated normal ABR thresholds to air-conducted clicks on the day of testing, and two were lost to follow-up. Thus, sensorineural hearing loss reasonably could be ruled out in 35 of the 48 infants participating in this study.

Results were obtained for 66 ears of the above infants; these fell into three general categories: 1) normal external and middle ear function (24 ears), 2) probable OM (25 ears), and 3) external auditory meatal atresia (16 ears). Middle ear status was determined from the results of day-of-test pneumatic otoscopy and/or tympanometry (220- and/or 660-Hz probe frequency), as well as prior physical examination by an otolaryngologist (atretic ears). Criteria for classifying an ear as probable OM depended primarily upon the presence of a type B tympanogram. Otoscopic results consistent with middle ear effusion resulted in placement into the OM group. Ears demonstrating type A or C tympanograms[21] were placed in the normal group.

Stimuli consisted of 500- and 2,000-Hz tones presented at 38.5/s through a Radioear B70A bone oscillator. The 500-Hz tones were shaped by use of an envelope with a linear 4.0-ms rise time, a 2.0-ms plateau, and a 4.0-ms fall time; the 2,000-Hz tones were shaped by a 1.0-ms rise time, a 1.0-ms plateau, and a 1.0-ms fall time. Behavioral thresholds (0 dB nHL) for these BC short duration tones obtained from six normal-hearing adults were 54 and 30 peak equivalent decibels (re: 1 dyne rms) for 500 and 2,000 Hz, respectively. Behavioral thresholds were obtained with the subject hand-holding the oscillator on his or her temporal bone. These thresholds are similar to those obtained by another laboratory for similar stimuli.[20] Stimuli were calibrated with a Bruel & Kjaer artificial mastoid (model 4930) and sound level meter (model 2203). Peak equivalent measures were obtained by matching the short duration tone's peak-to-peak amplitude with a continuous sine wave of the same frequency, and then recording the reading of the sound level meter for the continuous tone.[22]

The brain stem responses were recorded with

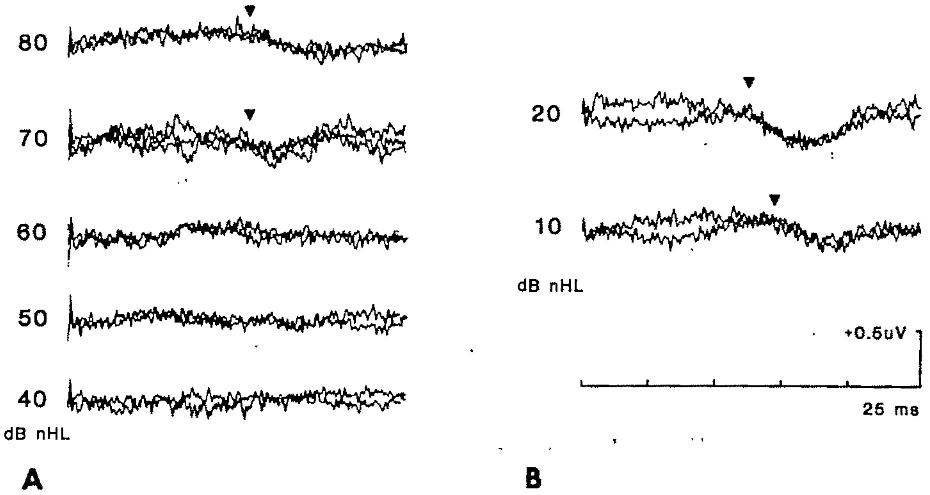

Fig 2. Brain stem responses to 500-Hz tones recorded from 6-month-old infant with unilateral atresia. Contralateral (normal) ear was masked with 88-dB SPL white noise. Auditory brain stem response threshold to 500-Hz air-conducted tones (70 dB nHL) is 50 to 60 dB above usual range of 10 to 20 dB nHL for normal thresholds. A) Air-conducted tones. B) Bone-conducted tones.

gold-plated cup electrodes placed at the vertex (Cz) and each mastoid (M1 and M2). A similar electrode placed on the forehead served as a ground. This setup allowed the simultaneous recording of two EEG channels: 1) vertex to left mastoid (Cz-M1), and 2) vertex to right mastoid (Cz-M2). Interelectrode impedances were less than 3,000 Ω. The EEG was amplified and filtered with a bandpass of 30 to 3,000 Hz (12 dB/octave slope). Trials containing amplitudes greater than ±25 μV were automatically rejected. Averaging was carried out by use of a 25-ms analysis time. At least two replications of 2,000 trials each were always obtained for a specific condition.

Testing was carried out in a double-walled sound-attenuating room (Industrial Acoustics Corp). All testing was carried out while the infants were in natural sleep or in chloral hydrate–induced sleep. In most cases, infants slept in a crib; occasionally they were held by their mothers. The bone oscillator was placed on an infant's temporal bone directly above (within 2.5 cm) the ear to be tested, and held in place by his or her parent. Bone oscillator pressure was not controlled among infants. Except where indicated, masking of the ear contralateral to oscillator placement was not attempted. Only results obtained without masking are included in the mean data.

Presence of a replicable brain stem response was visually determined by two of three observers experienced with tone-evoked ABRs. When present, four measures were obtained from each recording: 1) presence or absence of a replicable response within the analysis time following the end of the stimulus (later than 10 ms for 500 Hz, and later than 3 ms for 2,000 Hz); 2) amplitude of the maximum replicable deflection occurring within the analysis period; 3) presence or absence of a vertex-positive ABR wave V; and 4) latency of wave V. Statistical analyses were carried out for individual ears with repeated measures analyses of variance and Student's *t* tests. Results were considered significant if $p < .05$.

RESULTS

Ipsilateral Recordings. Figure 1 shows typical

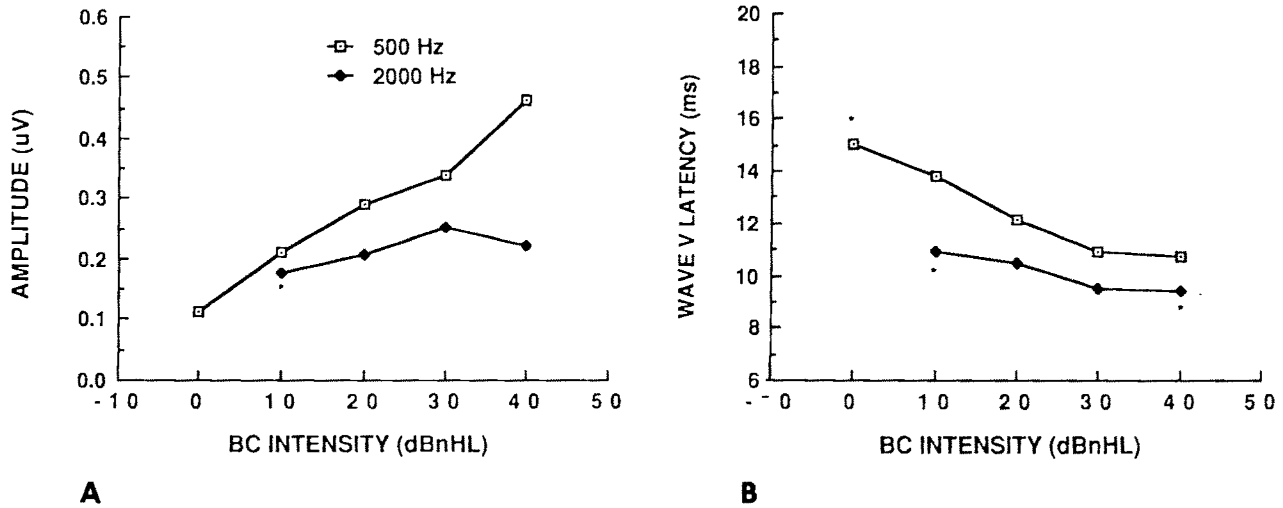

Fig 3. Mean results for all infants for 500- and 2,000-Hz bone-conducted tones. Masking of ears contralateral to bone oscillator placement was not employed. Asterisks — data points representing results of fewer than 10 ears. A) ABR maximum amplitude. B) Wave V latency.

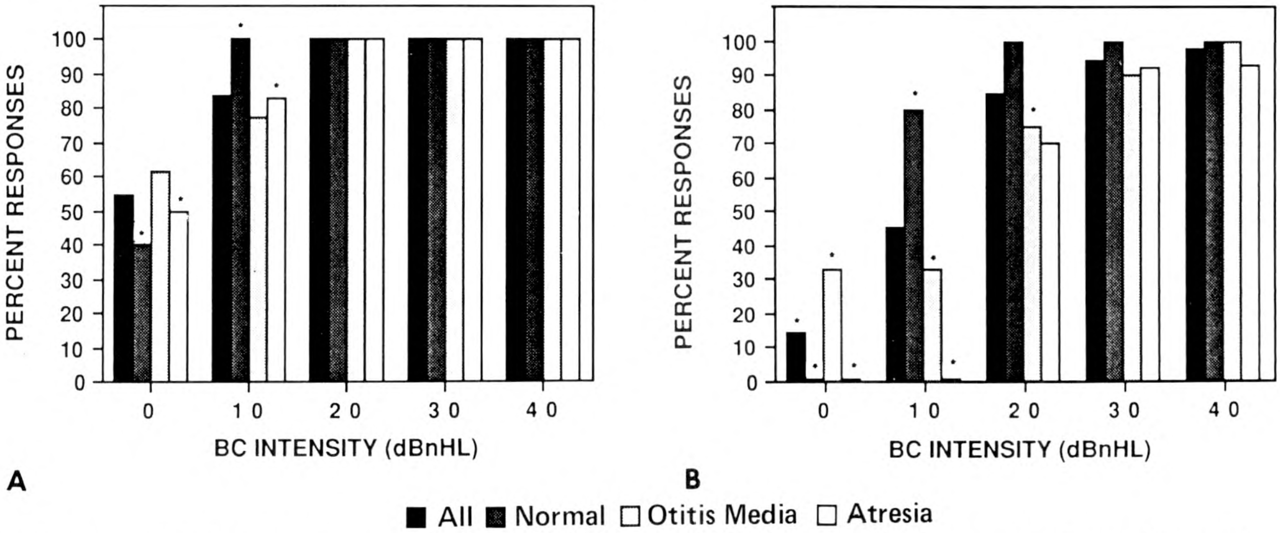

Fig 4. Cumulative brain stem response detectability for bone-conducted (BC) tones. Results for all ears combined, ears with normal middle ear status, ears with otitis media, and atretic ears are presented. Masking of ears contralateral to bone oscillator placement was not employed. Asterisks — results for fewer than 10 ears. A) 500-Hz tones. B) 2,000-Hz tones.

brain stem responses to 500- and 2,000-Hz BC tones recorded from a 4-month-old infant with normal middle ear status. Replicable responses can be detected at 40 through 10 dB nHL for the 500-Hz BC tones, and at 40 through at least 20 dB nHL (recordings were not obtained at 10 dB nHL) for the 2,000-Hz BC tones. The approximate latency of wave V in these waveforms is indicated by the arrows. For most subjects, however, the component easiest to discriminate is the vertex-positive to vertex-negative deflection that begins at the peak of wave V and continues for at least 3 to 8 ms. As demonstrated by this individual's results, wave V latency increases and amplitude decreases as the BC stimulus intensity is decreased. Wave V latency is longer for the 500-Hz BC stimuli; amplitudes are lower in response to the 2,000-Hz BC stimuli.

Figure 2 shows the brain stem responses to 500-Hz BC tones and responses to 500-Hz air-conducted tones recorded from a 6-month-old infant with unilateral atresia. In this case, the infant's contralateral (normal) ear was masked with 88-dB SPL white noise. This level of white noise is above that required for effective masking of the same stimuli in adults. The responses to the air-conducted tones demonstrate a threshold of 70 or 80 dB nHL, a level elevated 50 to 60 dB above the usual threshold for these stimuli.[3-5] In contrast, the responses to the BC tones demonstrate clear components at 20 and 10 dB nHL, suggesting that the cochlea of the atretic ear responds to low intensity, 500-Hz BC stimuli (assuming the contralateral ear was effectively masked).

The brain stem responses from the two infants presented above are typical of the results obtained from the larger group of infants participating in this study. Mean amplitude and latency results are presented in Fig 3 for the 500- and 2,000-Hz BC tones and reflect the pattern of results shown in Fig 1. The responses to 500-Hz BC tones are about 50% greater in amplitude than the responses to the 2,000-Hz BC tones ($t = 2.89$, $df = 52$, $p < .01$). The difference is greater at 40 dB nHL, when the mean 2,000-Hz amplitude decreases slightly from the 30-dB mean, indicating 2,000-Hz amplitude saturation above 30 dB nHL. The mean 500-Hz wave V latency (10.75 ms at 40 dB) is about 1.5 ms later than for the 2,000-Hz BC tones ($t = 2.41$, $df = 24$, $p < .05$). The slopes of the amplitude increase and latency decrease with increasing intensity are similar in response to the two stimuli, except for the 2,000-Hz amplitude saturation above 30 dB nHL. The latency shift with stimulus frequency is less than half that seen for responses to air-conducted tones in infants[3,5] and may indicate decreased frequency specificity for either the 500- or 2,000-Hz BC tones, or both.

Figure 4 presents the cumulative detectability of a replicable response versus intensity for the 500- and 2,000-Hz BC tones. Data for all ears combined are presented together with results for the three middle ear status categories. As would be expected from the amplitude results, responses to the 500-Hz BC tones are detectable at lower intensities (relative to adult behavioral threshold) than are those to the 2,000-Hz BC tones. The detectability of the responses for the different ear categories is essentially similar. These data demonstrate the feasibility of recording the ABR to BC tones from infants with normal cochlear sensitivity. Most of these infants, with or without conductive involvement, demonstrate responses to 500-Hz BC tones presented at 20 dB nHL (100%) and to 2,000-Hz BC tones presented at 30 dB nHL (94%).

Ipsilateral Versus Contralateral Recordings. Figure 5 shows the brain stem responses recorded in the

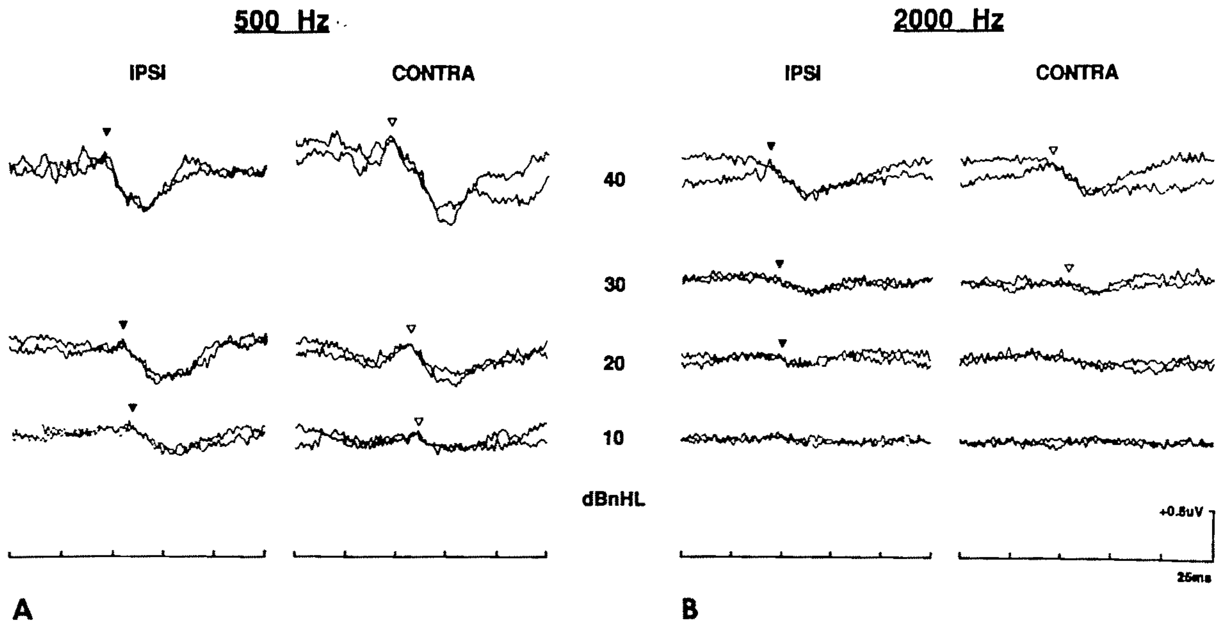

Fig 5. Brain stem responses recorded in ipsilateral (ipsi) and contralateral (contra) EEG channels in response to A) 500- and B) 2,000-Hz bone-conducted tones. Masking of ears contralateral to bone oscillator placement was not employed. Filled arrows — approximate ipsilateral wave V latency, open arrows — approximate contralateral wave V latency. A) Subject 4 months of age with OM. B) Subject 4 months of age with normal hearing.

vertex-to-ipsilateral mastoid and in the vertex-to-contralateral mastoid EEG channels obtained from two 4-month-old infants. The stimuli were 500- and 2,000-Hz BC tones. With the exception of the responses at 40 dB nHL, clear differences exist between the responses in the two channels, with ipsilateral responses being greater in amplitude and earlier in latency than those recorded in the contralateral channel. Response threshold is lower for the ipsilateral channel. These results are similar to those demonstrated previously for neonates' ABR to air-conducted clicks.[23,24] Unlike responses to air-conducted stimuli, however, the brain stem responses to the 40-dB nHL BC tones are similar in both channels, both at 500 and 2,000 Hz (Fig 5).

Figure 6 presents the mean ipsilateral and contralateral ABR latency and amplitude results for 500-Hz BC tones for all infants. Mean amplitudes are significantly lower (at 500 Hz: $F = 19.77$, $df = 1,46$, $p < .0002$; at 2,000 Hz: $F = 17.78$, $df = 1,30$, $p < .0005$) and wave V latencies significantly later (at 500 Hz: $F = 22.78$, $df = 1,21$, $p < .0002$; at 2,000 Hz: $F = 29.47$, $df = 1,17$, $p < .001$) in the contralateral channel recordings for the BC tones presented at 30 dB nHL and lower. At 40 dB nHL, the mean ipsilateral and contralateral amplitude differences just reached statistical significance for the 500-Hz BC tones ($t = 2.22$, $df = 11$, $p = .048$) but not for the 2,000-Hz BC tones ($t = 0.141$, $df = 9$, $p > .85$). In contrast, the mean wave V ipsilateral/contralateral

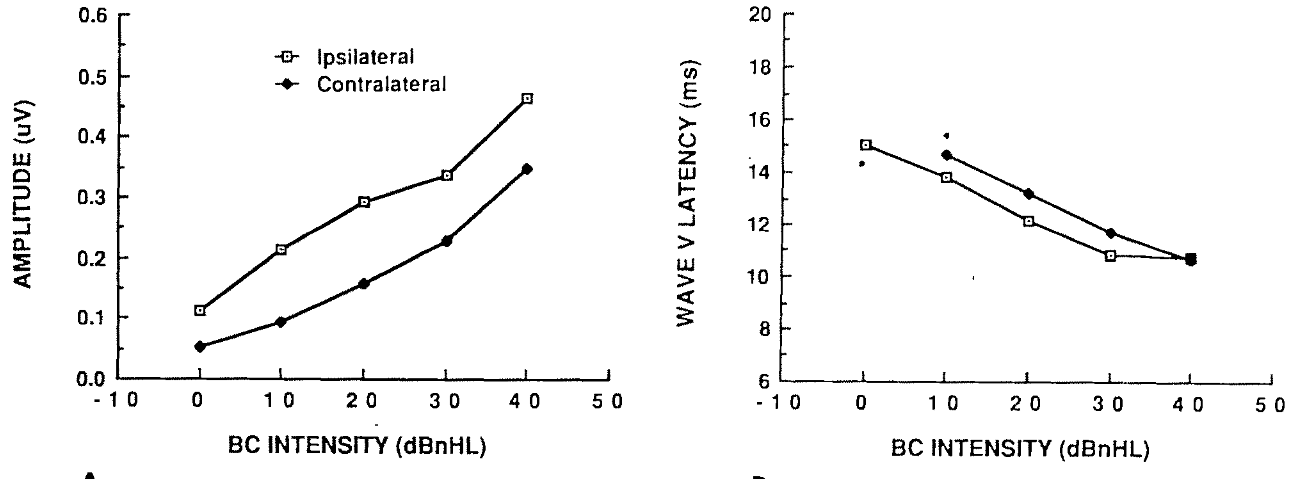

Fig 6. Mean ABR results for ipsilateral versus contralateral EEG channels. Stimuli were 500-Hz bone-conducted tones. Data represent mean for all infants. Ears contralateral to bone oscillator placement were not masked. Asterisks — data points representing results for fewer than 10 ears. A) Maximum amplitude. B) Wave V latency.

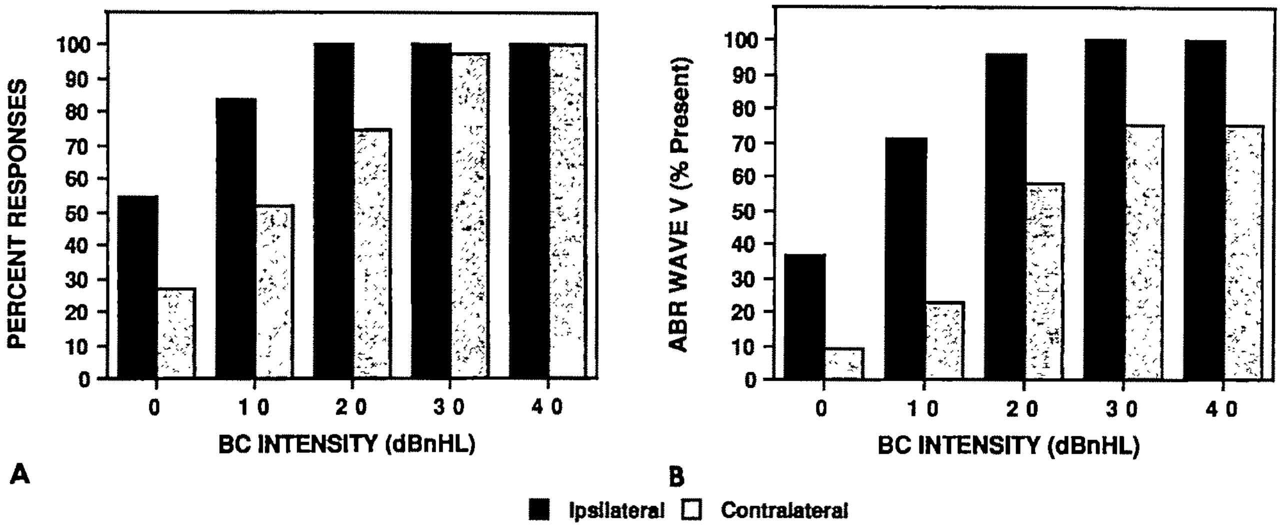

Fig 7. Cumulative A) brain stem response detectability and B) wave V detectability for ipsilateral and contralateral EEG channels. Stimuli were 500-Hz bone-conducted tones. Data represent results for all infants. Ears contralateral to bone oscillator placement were not masked.

40-dB nHL latency difference reached statistical significance for the 2,000-Hz BC tones ($t = 3.65$, $df = 7$, $p < .01$) but not the 500-Hz BC tones ($t = 0.82$, $df = 8$, $p > .4$).

On average, the contralateral channel results demonstrate poorer response detectability compared to the ipsilateral recordings (Fig 7A). This is true below 30 dB nHL for the 500-Hz BC tones and below 40 dB nHL for the 2,000-Hz BC tones. If only the detectability of an ABR wave V is considered (Fig 7B), differences between the responses recorded in the ipsilateral and contralateral EEG channels are heightened. In those cases in which a replicable response was seen with no detectable ABR wave V, the waveforms demonstrated either a vertex-negative component, near the ipsilateral wave V latency,[23] or a vertex-positive component similar in morphology but occurring either too late or too early to be wave V.

The ipsilateral/contralateral asymmetry of infants' brain stem responses might be helpful for determining which cochlea is the primary contributor to a response (when masking is not possible). The recordings shown in Fig 8 were obtained from a 9-month-old infant with normal middle ear status, and show her responses to 500-Hz air-conducted tones presented at 40 dB nHL (Fig 8A) and to 500-Hz BC tones presented at 20 dB nHL (Fig 8B).

When either the left ear or the left temporal bone was stimulated, the ipsilateral (Cz-M1) EEG channel demonstrates a clear response, whereas none is visible in the contralateral (Cz-M2) channel. When the earphone or oscillator is switched to the right ear, the response asymmetry makes a corresponding switch such that the response is now seen in the right (Cz-M2) channel. For the low intensity air-conducted stimulus, the recorded response represents only the response originating from the stimulated ear, and the corresponding right/left response changes are indicative of a change of the cochlea being stimulated. The similar ipsilateral/contralateral changes seen for BC stimuli also should represent a change in which cochlea is the primary contributor to the response.

The potential utility of these asymmetries is demonstrated in Fig 9, which shows the ipsilateral/contralateral ABR waveforms to 20 dB nHL 500- and 2,000-Hz BC tones recorded from a 3-month-old infant with bilateral external auditory meatal atresia. In contrast with the infant of Fig 8, it was not possible to provide masking noise to this patient's ears. As expected, his waveforms demonstrate changes in response asymmetry similar to those in Fig 8. These results thus suggest cochlear sensitivity to these 500- and 2,000-Hz BC tones bilaterally.

The above asymmetry reversal was investigated for 46 ears at 500 Hz and 28 ears at 2,000 Hz. In total, for 20-dB nHL 500-Hz BC tones, 94% of the ears demonstrated the expected response asymmetry (response greater and/or earlier ipsilaterally), 2% demonstrated equivocal results (amplitude and latency the same ipsilaterally and contralaterally), and 4% demonstrated opposite results (latency earlier and amplitude greater in contralateral channel). Similar results were seen for the 2,000-Hz BC tones presented at 30 dB nHL, with 93% demonstrating the expected asymmetry, 7% giving equivocal results, and none demonstrating opposite results. These data suggest the feasibility of employing the infant ABR asymmetries when determining the cochlear origin or "laterality" of a response.

DISCUSSION

This study demonstrates the feasibility of recording the ABR to BC tones for the purpose of demonstrating normal cochlear sensitivity. Most (94% to

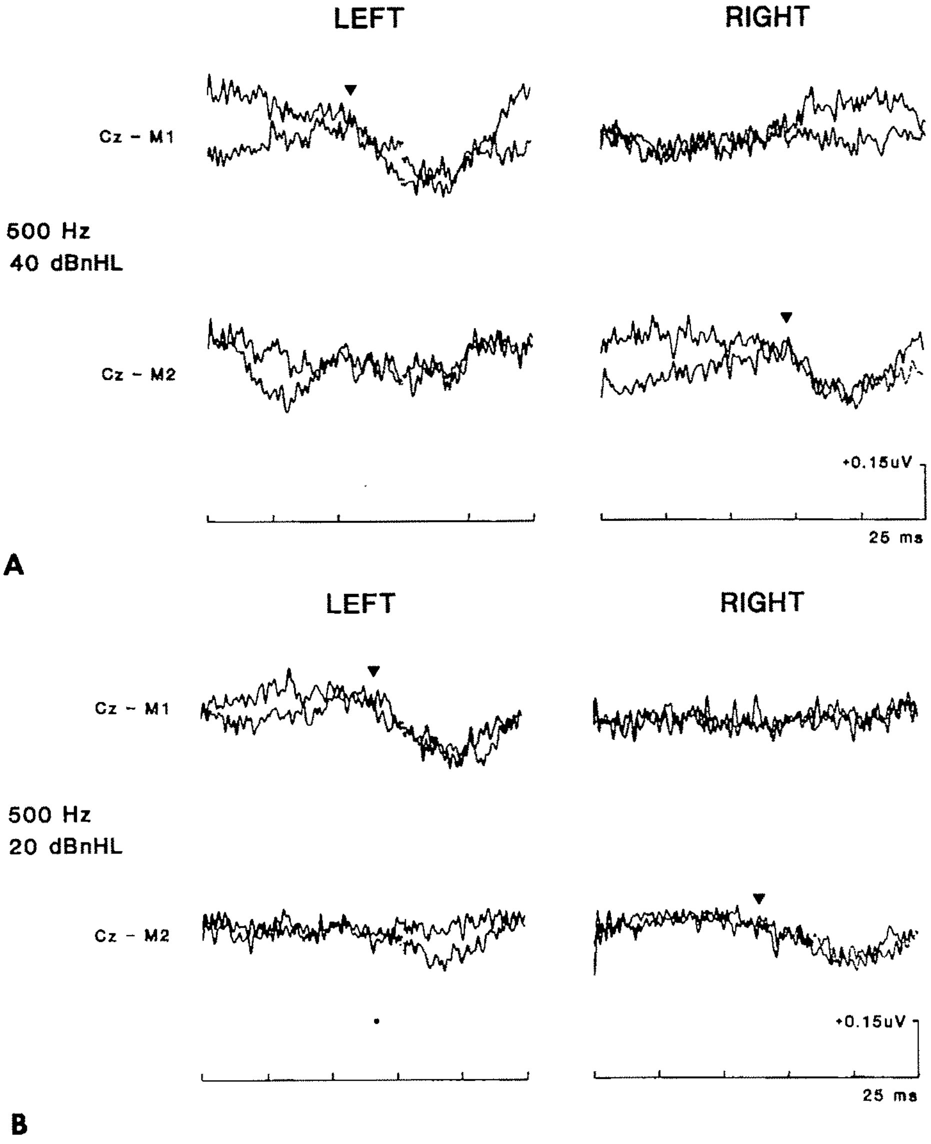

Fig 8. Brain stem responses recorded from 9-month-old subject with normal hearing by use of two-channel EEG recordings (Cz-M1, left; Cz-M2, right) for left-side and right-side stimulation by 500-Hz tones. Ear contralateral to earphone or bone oscillator placement was masked with 88-dB SPL white noise. Filled arrows — approximate ipsilateral wave V latency. A) Responses to 40-dB nHL air-conducted tones. B) Responses to 20-dB nHL bone-conducted tones.

100%) infants with normal cochlear sensitivity will demonstrate replicable ABRs when 20-dB nHL 500-Hz or 30-dB nHL 2,000-Hz BC tones are presented to the temporal bone. The absence of a response to these stimuli suggests the presence of sensorineural impairment; the presence of a response suggests normal cochlear sensitivity at least for the better ear. Although the extent to which this technique may be applied to infants with sensorineural or mixed impairments was not investigated, reliable results were found for infants with normal middle ear function, infants with OM, and infants with unilateral or bilateral external auditory meatal atresia.

The ipsilateral/contralateral amplitude and latency asymmetries seen in infants' ABRs to air-conducted stimuli[16,23,24] are also present in their responses to BC stimuli. These asymmetries may help determine which cochlea is the primary contributor to the recorded ABR. This is particularly useful, as it is often difficult to apply masking to an infant's contralateral ear while he or she sleeps. It is also difficult to determine the required masking levels for individual infants.

The ABR to BC stimuli is unique in its ability to assess bilateral conductive impairment, especially bilateral atresia, when masking is either impossible or very difficult. The inclusion of BC tonal stimuli supplements the information provided by evaluating ipsilateral/contralateral ABR wave I asymmetries in response to BC clicks, in which the presence of wave I indicates contribution of the cochlea ipsilateral to wave I,[25] by providing information for specific frequencies. Further, the later ipsilateral/contralateral asymmetries investigated in the present study may remain clear even when wave I is not recordable, as is often the case when high frequency impairment is present, when low intensity stimuli are used, or during poor signal-to-noise recording conditions.

Little is known of the effects of maturation of

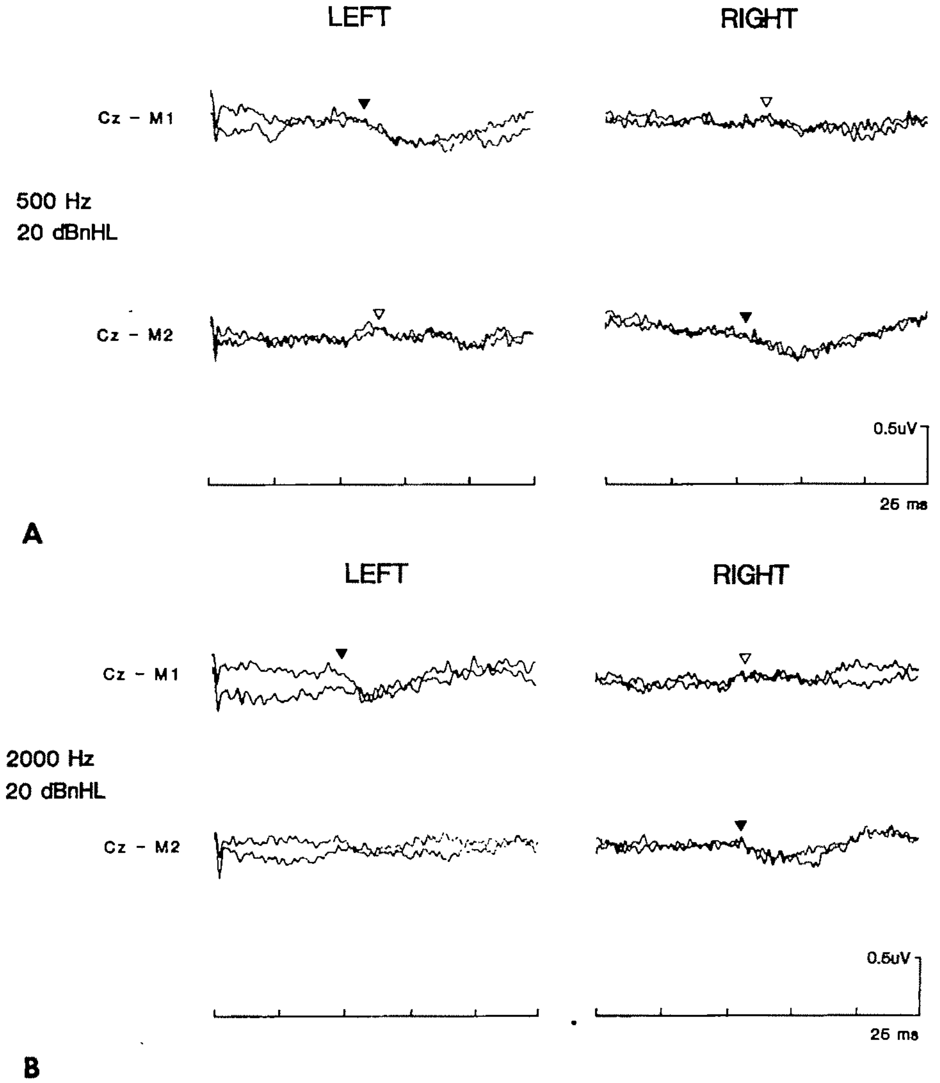

Fig 9. Brain stem responses recorded from 3-month-old infant with bilateral atresia by use of two-channel EEG recordings (Cz-M1, left; Cz-M2, right) for left-side and right-side bone-conducted stimulation. Ear contralateral to bone oscillator placement could not be masked. Reversal in response asymmetry with change in bone oscillator placement indicates bilateral cochlear sensitivity to these stimuli. Filled arrows — approximate ipsilateral wave V latency, open arrows — approximate contralateral wave V latency. A) 500-Hz tones. B) 2,000-Hz tones.

either the calvarium or the brain stem auditory pathways on these results. The contralateral ABR (wave V) to air-conducted clicks in older children and adults is nearly identical to that recorded ipsilaterally; thus the wave V asymmetries seen in the infants in this study (2 to 24 month of age) would decrease as they mature.[16] Yang and his colleagues[17] have shown maturational changes in the ipsilateral ABR to BC clicks that suggest decreasing interaural attenuation of the click from 25 to 35 dB in neonates, 15 to 25 dB in 1-year-olds, and 0 to 10 dB in adults, occurring presumably as a result of maturation of the cranium and membranous tissues. The similarity of the ipsilateral and contralateral responses to 40 dB nHL BC tones, however, suggests the process is more complex than simple attenuation. Further investigation of the effects of development on these results is required.

The results of the present study are consistent with the suggestion that masking of the contralateral ear may not be required for low intensity BC stimuli in young infants.[17] By 40 dB nHL, however, both cochleas appear to be stimulated and masking may be necessary. Further study may indicate that the presence of similar ipsilateral and contralateral responses (ie, a lack of asymmetry) at this intensity in young infants indicates cochlear sensitivity to the BC stimulus bilaterally.

Infants' brain stem responses to 500-Hz BC tones are greater in amplitude and detectable at lower intensities than those to 2,000-Hz BC tones. Similar results have been demonstrated for adult subjects.[20] This finding contrasts with the ABR to air-conducted tones, in which thresholds are lower for 2,000-Hz tones than for 500-Hz tones.[2,4,5,10] These results may be related to the frequency response of the bone oscillator[17,18] and to skull transmission characteristics.[17] They also may reflect activation of greater cochlear area by 500-Hz BC tones. Overall, thresholds for the 500- and the 2,000-Hz BC tones are lower (relative to adult behavioral threshold) than those obtained for air-conducted tones. Although the nHL levels obtained in this study are within 2 to 5 dB of those obtained elsewhere,[20] and the 500-Hz versus 2,000-Hz threshold difference is similar to existing pure tone audiometric BC calibration standards,[26] adult reference levels for BC stimuli may not be applicable to young infants. The results of the present study and those of Yang et al[17] suggest that these BC stimuli are more effective ("louder") in young infants than in adults. If this is true, data based upon ABR detectability (Fig 4) in normal infants may be the preferred means of determining "0 dB nHL."

Although the results of this study are encouraging, several limitations and important unknown factors exist for this technique. More-detailed investigations of possible group differences in the BC ABR results obtained from patients with differing conductive losses will require knowledge of their air-conducted versus BC results. The short duration stimuli transduced through a B70A bone oscillator have a dynamic range of only 45 to 60 dB,[18] and therefore they are limited when applied to patients with sensorineural hearing impairment. The effects of sensorineural hearing impairment on the ipsilateral/contralateral asymmetries of ABR to BC tones awaits investigation. Further information is needed concerning the stimulus and other subject dependencies of the ipsilateral/contralateral asymmetries. Little is known of the spectral content of BC stimuli at the cochlea or how this may change as an infant's skull matures. Finally, investigation of the frequency and place specificity of these BC tone ABR measures is needed. Although they are reasonably frequency-specific in adults,[20] the small difference between infant ABR latencies to 500- and 2,000-Hz BC tones (Fig 3) may indicate decreased frequency specificity.

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REFERENCES

1. Eggermont JJ. The inadequacy of click-evoked auditory brainstem responses in audiological applications. Ann NY Acad Sci 1982;388:707-9.

2. Hyde ML. Frequency-specific BERA in infants. J Otolaryngol 1985;14(suppl 14):19-27.

3. Suzuki J-I, Kodera K, Yamada O. Brainstem responses in newborns and hearing-impaired infants. In: Starr A, Rosenberg C, Don M, Davis H, eds. Sensory evoked potentials. 1. An international conference on standards for auditory brainstem response (ABR) testing. Milan, Italy: CRS Amplifon, 1984:85-93.

4. Stapells DR, Picton TW, Perez-Abalo M, Read D, Smith A. Frequency specificity in evoked potential audiometry. In: Jacobson JT, ed. The auditory brainstem response. San Diego: College Hill, 1985:147-77.

5. Stapells DR. Auditory brainstem response assessment of infants and children. Semin Hear 1989;10:229-51.

6. Picton TW, Ouellette J, Hamel G, Smith AD. Brainstem evoked potentials to tonepips in notched noise. J Otolaryngol 1979;8:289-314.

7. Durieux-Smith A, Picton TW, Edwards CG, MacMurray B, Goodman JJ. Brainstem electric-response audiometry in infants of a neonatal intensive care unit. Audiology 1987;26:284-97.

8. Kodera K, Yamane H, Yamada O, Suzuki J-I. Brain stem response audiometry at speech frequencies. Audiology 1977;16:469-79.

9. Kileny P. The frequency specificity of tone-pip evoked auditory brainstem responses. Ear Hear 1981;2:270-5.

10. Klein AJ. Properties of the brain-stem response slow-wave component. I. Latency, amplitude, and threshold sensitivity. Arch Otolaryngol 1983;109:6-12.

11. Klein AJ. Properties of the brain-stem response slow-wave component. II. Frequency specificity. Arch Otolaryngol 1983;109:74-8.

12. Stapells DR, Picton TW. Technical aspects of brainstem evoked potential audiometry using tones. Ear Hear 1981;2:20-9.

13. Picton TW, Durieux-Smith A. The practice of evoked potential audiometry. Otolaryngol Clin North Am 1978;11:263-82.

14. Mauldin L, Jerger J. Auditory brain stem evoked responses to bone-conducted signals. Arch Otolaryngol 1979;105:656-61.

15. Weber BA. Masking and bone conduction testing in brainstem response audiometry. Sem Hear 1983;4:343-52.

16. Picton TW, Taylor MJ, Durieux-Smith A, Edwards CG. Brainstem auditory evoked potentials in pediatrics. In: Aminoff MJ, ed. Electrodiagnosis in clinical neurology. 2nd ed. New York: Churchill Livingstone, 1986:505-34.

17. Yang EY, Rupert AL, Moushegian G. A developmental study of bone conduction auditory brain stem response in infants. Ear Hear 1987;8:244-51.

18. Schwartz DM, Larson V, DeChicchis AR. Spectral characteristics of air and bone transducers used to record the auditory brainstem response. Ear Hear 1985;6:274-7.

19. Boezeman EHJF, Kapteyn TS, Visser SL, Snel AM. Comparison of the latencies between bone and air conduction in the auditory brain stem evoked potential. Electroencephalogr Clin Neurophysiol 1983;56:244-7.

20. Kramer SJ, Stapells DR. Frequency-specific bone-conducted auditory brainstem responses. ASHA 1987;29(10):87.

21. Jerger J. Clinical experience with impedance audiometry. Arch Otolaryngol 1970;92:311-24.

22. Stapells DR, Picton TW, Smith AD. The calibration of click intensity. In: Starr A, Rosenberg C, Don M, Davis H, eds. Sensory evoked potentials. 1. An international conference on standards for auditory brainstem response (ABR) testing. Milan, Italy: CRS Amplifon, 1984:35-8.

23. Edwards CG, Durieux-Smith A, Picton TW. Neonatal auditory brainstem responses from ipsilateral and contralateral recording montages. Ear Hear 1985;6:175-8.

24. Salamy A, Eldredge L, Wakeley A. Maturation of contralateral brain-stem responses in preterm infants. Electroencephalogr Clin Neurophysiol 1985;62:117-23.

25. Jahrsdoerfer RA, Yeakley JW, Hall JW, Robbins KT, Gray LC. High-resolution CT scanning and auditory brain stem response in congenital aural atresia: patient selection and surgical correlation. Otolaryngol Head Neck Surg 1985;83:292-8.

26. American National Standards Institute. Reference equivalent threshold levels for audiometric bone vibrators. New York: ANSI S3.26-1981.

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AUDIOLOGIC THRESHOLD MONITORING OF PATIENTS RECEIVING OTOTOXIC DRUGS

PRELIMINARY REPORT

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An effort was made to determine the efficacy of auditory threshold monitoring of patients receiving ototoxic drugs. Forty-four patients treated with either tobramycin or vancomycin for osteomyelitis were tested at the beginning of treatment, following treatment, and twice weekly during treatment when possible. All patients had renal function carefully monitored. Peak and trough drug levels were kept out of the toxic range throughout the study. In no patient did indisputable ototoxicity occur, and therefore, no conclusion about the most efficacious schedule for auditory monitoring of patients receiving ototoxic drugs was made, and what constitutes a significant intratherapeutic threshold shift is still in question. Until further data are collected, monitoring of renal function and peak and trough drug levels, as well as patient counseling, is recommended. Pretherapy and posttherapy auditory monitoring and intratherapeutic monitoring of high-risk patients and those who develop aural symptoms may prove beneficial.

KEY WORDS — ototoxicity, peak and trough levels, renal function.

INTRODUCTION

Two instances in which patients suffered sensorineural hearing loss following parenteral treatment with ototoxic drugs were recently litigated in north central Texas. The plaintiffs each alleged that intratherapeutic monitoring could have provided early warning and therefore would have deterred serious hearing loss, and that lack of auditory monitoring constituted a breach in the standard of care. The defense argued that the ototoxic drugs were used as a lifesaving measure and that no standard of care existed regarding intratherapeutic auditory monitoring of patients receiving ototoxic drugs, an argument supported by the literature. Thompson and Northern[1] readily admitted that there is no firm agreement on the efficacy of routine auditory monitoring and that its usefulness remains in question. Lerner and Matz[2] agreed that the role of auditory monitoring in the prevention of ototoxic hearing loss was uncertain, and acknowledged that insufficient information was available to establish any firm guidelines. Despite these publications and none to the contrary, in both cases the plaintiff's arguments prevailed and substantial settlements against the physician and the hospital were reached.

As a result of these legal decisions and in view of the fact that no standard of practice for auditory monitoring during the use of ototoxic drugs is apparent to the authors, members of the American Otological Society, Inc, were consulted for their opinions. Of the 110 questionnaires mailed, 79 were completed and returned. Most respondents, in addition to completing the questionnaire, acknowledged that little or no agreement existed in the literature, and that there was a definite lack of well-controlled studies and insufficient information available to reach any firm conclusions. Less than 4% (3/79) of those who responded felt that pretreatment, posttreatment, and daily during-treatment monitoring of auditory thresholds was necessary. An equally small number (4/79) felt that no monitoring at all was required. The majority of respondents (52%) preferred biweekly monitoring of auditory thresholds in addition to pretherapy and posttherapy measurements, but 32% felt that weekly monitoring was sufficient. Six of those answering the questionnaire (8%) felt that intratherapeutic monitoring was unnecessary as long as baseline thresholds were obtained prior to and following therapy. Almost all respondents volunteered that careful dosing and careful monitoring of peak and trough drug levels along with careful monitoring of renal function and insightful pretherapy patient counseling were the most important aspects of good patient care when the parenteral use of ototoxic drugs was required. Almost all respondents also felt that a clinical change in the patients' aural symptoms (tinnitus, fullness, balance disturbance, or hearing loss) should mandate institution of auditory testing if it is not already in progress.

In an effort to help determine the efficacy of intratherapeutic auditory monitoring of patients on parenteral ototoxic drugs, a prospective study was designed. The chosen interval for monitoring was

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that most frequently recommended by the members of the American Otological Society, Inc, who answered the questionnaire (ie, pretherapy, posttherapy, and biweekly during therapy).

MATERIALS AND METHODS

Forty-four consecutive patients with osteomyelitis requiring parenteral treatment with ototoxic antibiotics (tobramycin sulfate or vancomycin) were studied. Nineteen patients were female, 25 patients were male, and the average age was 46 years (range, 16 to 77 years). Preoperatively, the patients were staged for the type of osteomyelitis according to the classification of Cierny et al.[3] Prior to treatment all patients had the following studies performed: erythrocyte sedimentation rates, SMAC (sodium, potassium, chloride, blood urea nitrogen [BUN], creatinine, glucose, and carbon dioxide), complete blood cell count, culture and sensitivity of the wound when possible, triphasic technetium 99m bone scan, and indium-labeled white blood cell studies, as well as computed tomography, magnetic resonance imaging, and plain x-ray studies of the involved area. Creatinine clearance was performed if the BUN or creatinine was elevated. The patients then underwent radical debridement of the infected bone and soft tissue. Deep samples for culture were obtained, antibiotic-impregnated beads were placed (vancomycin or tobramycin, depending on pretherapeutic cultures and sensitivity), soft tissue coverage was performed, and a Groshung catheter was inserted (G. Maale and J. Peloza, unpublished data).

Intravenous injections of antibiotics were started, again based on preoperative cultures if available. If preoperative cultures were not available, patients were started on a regimen of Ancef and tobramycin until the results of the intraoperative cultures were available. All patients received either vancomycin or tobramycin throughout the course of therapy, but none received two ototoxic drugs simultaneously. Antibiotic dosing was determined by the bayesian and least-squares methods that are based on lean body weight and renal function.[4-6] Peak and trough antibiotic levels were determined weekly for tobramycin and vancomycin, and serum BUN and creatinine levels were determined biweekly throughout therapy. Two weeks after the initial procedure, the patients were taken back to the operating room for additional radical debridement, additional obtaining of samples for culture, and removal of the antibiotic-impregnated beads. If signs of infection persisted, antibiotic-impregnated beads were reimplanted and removed after an additional 2 weeks, with further debridement at that time. If no signs of persistent infection existed, the wound was irrigated copiously and definitive reconstruction was performed. Intravenous antimicrobial therapy was continued for 6 weeks after the final surgical procedure.

Audiologic threshold testing was performed by a certified clinical audiologist and was begun within 48 hours of drug initiation and discontinued within 48 hours of treatment completion. Patients were tested biweekly at bedside, when their condition permitted, on a Maico MA41 portable audiometer. Patients who continued therapy at home reported to our office for monitoring and were tested on a Grason Stadler GS1-16 clinical audiometer. Pure tone air conduction threshold testing was performed at 2,000, 3,000, 4,000, 6,000, and 8,000 Hz. Low frequency testing results were not used because low frequency ambient room noise rendered those results inaccurate.[1] Bone conduction testing at 2,000 and 4,000 Hz was performed at the initial evaluation and at subsequent evaluations if an air conduction threshold shift was observed. Aural symptoms that developed during treatment were recorded.

RESULTS

The 44 patients underwent a total of 374 auditory threshold tests for an average of 8.5 tests per patient Patient debilitation and the effects of anesthesia in those seen shortly after debridement prohibited consistent intratherapeutic biweekly testing in all patients. Ten of the 44 patients suffered an increased threshold of at least 15 dB in one frequency, a finding felt to be significant for ototoxicity by Thompson and Northern.[1] Thirteen of the patients, however, experienced an improved threshold of at least 15 dB in one frequency. In two patients, a 15-dB increase in threshold occurred in the ear contralateral to the one that experienced a 15-dB decrease in threshold, and in one patient, a 15-dB increase in threshold at one frequency was followed by a 15-dB decrease in threshold at the next frequency tested. These findings made a 15-dB change in one frequency seem of questionable significance in the study of ototoxicity and, therefore, average threshold changes were computed for the five frequencies tested (see Table). Seven patients (nine ears) demonstrated an average increase of 5 dB or more per frequency in the five frequencies tested, whereas in eight patients (nine ears) there was a similar 5-dB average improvement. No patient had a decrease in auditory threshold of 10 dB or greater at three consecutive frequencies, and in no case was the antibiotic treatment altered in any way as the result of these shifts. The threshold shifts were not associated with aural symptoms and did not progress.

There appeared to be no association between patient sex and the predisposition for auditory threshold change, nor could any relationship be found between preexisting hearing loss and threshold change. Peak and trough levels for both tobramycin and vancomycin never reached the toxic range in any patient. Total dosages ranged between 0.48 g and 34.89 g for tobramycin and between 1.8 g and 137.75 g for vancomycin and appeared to have no relationship to change in auditory threshold. Dur-

SUMMARY OF OTOTOXIC DRUG THERAPY AND THRESHOLD CHANGE

Pt No.	*Age*	*Sex*	*Drug*	*Total Dose (g)*	*Creatinine Level During Therapy*	*Threshold Change During Treatment**	
						Right Ear	*Left Ear*
1	35	F	Tobramycin	5.09	Increased†	5	5
2	48	F	Vancomycin	66.0	NC	0	0
3	69	F	Tobramycin	0.485	Increased†	−4	−9
4	38	F	Tobramycin	0.800	NC	−3	−3
5	23	F	Vancomycin	137.75	NC	−2	−2
6	55	F	Vancomycin	22.25	Increased†	−1	−1
7	37	M	Tobramycin	1.12	NC	0	−1
8	63	M	Tobramycin	1.44	NC	0	−1
9	62	M	Tobramycin	36.40	Increased†	0	0
10	50	M	Vancomycin Tobramycin	71.25 2.64	NC	4	−4
11	39	M	Vancomycin	21.10	NC	−1	1
12	38	F	Vancomycin	8.06	NC	−12	−4
13	77	F	Vancomycin	32.45	NC	5	13
14§	57	F	Vancomycin Tobramycin	42.2 0.99	NC	−6	−3
15	45	M	Vancomycin	28.5	NC	2	9
16	52	M	Tobramycin	29.6	NC	3	7
17	57	M	Vancomycin	49.59	NC	−5	3
18	56	F	Tobramycin	6.55	Increased†	−2	3
19	64	M	Tobramycin	3.5	NC	5	−5
20	69	F	Tobramycin	9.16	NC	3	6
21	48	M	Vancomycin	90.25	NC	−4	3
22§	67	M	Tobramycin	2.79	NC	4	8
23	32	F	Tobramycin	21.68	NC	−2	2
24	31	M	Tobramycin	7.12	NC	1	1
25	63	M	Tobramycin	5.25	Increased†	3	1
26	43	F	Tobramycin	1.65	Increased†	−1	2
27	59	F	Tobramycin	7.14	NC	0	1
28	34	M	Tobramycin	21.55	NC	0	0
29	61	M	Tobramycin	6.67	Increased†	−1	−4
30∫	32	F	Vancomycin	1.8		−10	−6
31	31	F	Tobramycin	0.68	NC	−3	−5
32	35	M	Tobramycin	21.55	NC	−1	−3
33	36	M	Tobramycin	34.89	NC	−3	−3
34	28	M	Tobramycin	3.3	NC	1	0
35	36	M	Vancomycin	40.6	NC	−2	0
36	39	F	Vancomycin	24.8	NC	0	0
37	60	F	Vancomycin	28.02	NC	3	2
38	17	F	Vancomycin	83.51	NC	3	1
39	52	M	Vancomycin	75.5	NC	0	−1
40	62	M	Tobramycin	16.82	NC	1	0
41	34	M	Tobramycin	6.8	NC	2	−1
42	16	M	Tobramycin	14.0	NC	−5	−1
43	31	M	Tobramycin	7.12	NC	1	0
44	57	F	Vancomycin	31.0	NC	−1	0

Pretreatment renal function of all patients except patient 30 was within normal limits.

NC — no change.

*Average threshold change in decibels per frequency over five frequencies tested.

†Drug therapy stopped because of increased creatinine level.

§Developed tinnitus during therapy.

∫Had renal failure and dialysis.

ing therapy, eight patients showed evidence of alteration in renal function requiring changes in their dosing, but as with total dosage, no relation between change in renal function and decrease in auditory threshold could be identified. Patients who suffered an average hearing loss of 5 dB or more per frequency in at least one ear, however, were 58 years of age on average, as compared to the average age of 46 years for the study population as a whole. Although the numbers are small, this suggests that advancing age, independent of renal function or preexisting hearing loss, may predispose one to ototoxicity.

DISCUSSION

The results of this preliminary study show a completely random data scatter and no clear-cut ototoxicity except, perhaps, in association with aging. We believe that not only is routine auditory threshold monitoring of patients receiving ototoxic drugs not of proven efficacy, but that no clear guidelines as to what represents a significant change in hearing under these most adverse conditions exist. Both drugs used in this study, tobramycin and vancomycin, frequently are needed in severe infections as lifesaving or limb-saving medications, and it is essential to understand their individual properties. All aminoglycosides consist of an amino sugar linked to another moiety by a glycoside bond. All members of the aminoglycoside family have relatively broad-spectrum antimicrobial coverage and are used topically or by injection because of their poor absorption through the gastrointestinal tract. All members of this family have potential for both nephrotoxicity and ototoxicity.[7] Tobramycin is an aminoglycoside that has the potential to cause vestibular as well as cochlear injuries. It crosses the blood-brain barrier poorly, and therefore its presence in the inner ear must occur through the vascular route. Serum levels are dependent not only upon dosage but upon renal function.[8] High frequency, steeply sloping sensorineural hearing loss is the early audiologic finding in patients suffering cochlear ototoxicity, and patients frequently complain of tinnitus before hearing loss. Because of the drug's slow clearance from the inner ear, these manifestations of toxicity may not occur until after administration of the drug has been stopped.[7]

Vancomycin, a narrow-spectrum antibiotic produced by *Streptomyces orientalis*, may also be lifesaving and is effective against gram-positive cocci. It has been reported to be especially ototoxic in cases complicated by renal failure or in which other potentially ototoxic drugs are being used.[7] There is little experimental information about the ototoxicity of vancomycin, since it exerts its antimicrobial activity by interfering with cell wall synthesis, a process that is not ongoing in the inner ear.[8]

The conclusions drawn from the results of our study on use of these two drugs are in agreement with those of Thompson and Northern,[1] who stated that routine auditory monitoring of patients receiving ototoxic drugs is unnecessary unless the patients are at high risk. We included in our study 1) patients with impaired renal function, 2) patients receiving high doses of ototoxic drugs for an extended period of time, 3) patients with unacceptably high peak and trough drug levels during treatment, 4) patients taking more than one ototoxic drug at a time, 5) patients with preexisting hearing loss or severe visual impairment, and 6) patients who develop aural symptoms during therapy.

These conclusions are also in keeping with those of Lerner and Matz,[2] who suggested guidelines for monitoring patients taking ototoxic drugs, although they admitted that sufficient information to support their guidelines was lacking. They stressed the importance of monitoring renal function, as well as peak and trough levels of the drug in use, but were far less emphatic about the role of auditory monitoring in the prevention of hearing loss. Perhaps because of our small sample size and the careful control of peak and trough levels, no association could be identified between renal function or total drug dosage and ototoxicity in our patient population. Last, an effort was made in our study to find an association between patient age and ototoxicity, as well as any correlation between preexisting hearing loss and the patients' susceptibility to ototoxicity. Although suggestions of such predisposition have been made in the literature, they could be corroborated only with advancing age in our patients and not with preexisting hearing loss.[9,10] This again may be due to the small sample size and the fact that peak and trough drug levels never reached the toxic range.[11]

There are two primary purposes for auditory threshold monitoring of patients receiving ototoxic drugs. The first purpose is to recognize the earliest threshold change possible in hopes of determining further loss, and the second is to identify hearing loss for medical-legal reasons and for rehabilitation. In order to detect the earliest threshold change in hopes of deterring further loss, super–high-frequency auditory testing must be performed, since the earliest threshold changes with ototoxic drugs occur in the very high frequencies and are often asymptomatic.[2] Bedside super–high-frequency auditory monitoring in the very sick patient, however, currently is not efficacious, since a reliable, quick, inexpensive, portable super–high-frequency audiometer is not yet available. The problem as to what constitutes a significant auditory threshold shift in these sick and difficult-to-evaluate patients is even greater in super–high-frequency audiometric testing than in standard monitoring. Further, since the initial medical indication for ototoxic drugs may still mandate their use and since further auditory impairment may occur following cessation of ototoxic drugs, such super–high-frequency testing is not felt to be cost-effective at this time.[1,2]

The mere identification of hearing loss when it occurs over the course of treatment for medical-legal purposes and for the purpose of rehabilitation can be accomplished in a rather cost-effective manner, although it may be difficult, at best, in the seriously ill patient. Fairly inexpensive portable audiometers now exist, and despite ambient bedside noise, fairly accurate baseline thresholds between 2,000 and 8,000 Hz can be obtained pretherapy at the bedside in a short period of time.[1,2] Posttherapy auditory thresholds can be tested under ideal circumstances about 6 weeks after treatment in a sound booth with use of contemporary equipment for a final auditory threshold determination. To address the concept of hearing loss identification in anticipation of rehabilitation, one can postpone intratherapeutic monitoring until aural symptoms arise. Although it has been shown that patients' aural symptoms may be inaccurate in predicting the exact onset of sensorineural hearing loss, symptoms definitely should become apparent by the time rehabilitation becomes appropriate. Bedside monitoring after aural symptoms have developed may very well prove efficacious.

SUMMARY

Forty-four consecutive patients receiving intravenous ototoxic drugs for a minimum of 8 weeks had pretherapy and posttherapy auditory threshold monitoring as well as biweekly monitoring when possible throughout their treatment course. Unfortunately, the results of this preliminary study represent a complete random data scatter with no clear-cut ototoxicity and no highly susceptible target groups for ototoxicity being identified except, perhaps, patients with advancing age. This leaves in question the efficacy of routine intratherapeutic auditory threshold monitoring. In addition, the study has raised questions regarding clear guidelines as to what represents a significant intratherapeutic change in hearing under the adverse condition in which ototoxic drugs are used. While additional prospective studies are underway to help answer both of these questions, we recommend careful drug dosing and monitoring of peak and trough drug levels in all patients undergoing treatment with ototoxic drugs, as well as careful monitoring of renal function and insightful pretherapy patient counseling. We further recommend pretherapy auditory threshold testing, as well as auditory threshold testing 6 weeks after the completion of antibiotic therapy. Intratherapeutic auditory threshold monitoring should be reserved for those patients who are over 50 years of age, those who have a clinical change in their aural symptoms, and those who have peak and trough drug levels in the toxic range. Monitoring is also recommended for those patients with poor renal function and for those who are receiving two or more ototoxic drugs simultaneously.

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REFERENCES

1. Thompson PL, Northern JL. Audiometric monitoring of patients treated with ototoxic drugs. In: Lerner SA, Matz GJ, Hawkins JE Jr, eds. Aminoglycoside ototoxicity. Boston: Little, Brown, 1981:237-45.

2. Lerner SA, Matz GJ. Suggestions for monitoring patients during treatment with aminoglycoside antibiotics. Otolaryngol Head Neck Surg 1979;87:222-8.

3. Cierny G III, Mader JT, Penninck JJ. A clinical staging system for adult osteomyelitis. Contemp Orthop 1985;10:17-37.

4. Burton ME, Chow MSS, Platt DR, Day RB, Brater DC, Vasko MR. Accuracy of bayesian and Sawchuk-Zaske dosing methods for gentamicin. Clin Pharm 1986;5:143-9.

5. Uaamnuichai M, Day RB, Brater DC. Bayesian and least-squares methods for vancomycin dosing. Am J Med Sci 1987;294:100-4.

6. Burton ME, Brater DC, Chen PS, Day RB, Huber PJ, Vasko MR. A bayesian feedback method of aminoglycoside dosing. Clin Pharmacol Ther 1985;47:349-57.

7. Sande MA, Mandell GL. Antimicrobial agents. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. The pharmacological basis of therapeutics. New York: Macmillan, 1985; 1150-69, 1170-98.

8. Stringer SP, Meyerhoff WL, Wright CG. Ototoxicity. In: Paparella MM, Shumrick D, Meyerhoff WL, eds. Otolaryngology. 3rd ed. Philadelphia: WB Saunders (in press).

9. Humes LE. Noise-induced hearing loss as influenced by other agents and by some physical characteristics of the individual. J Acoust Soc Am 1984;76:1318-29.

10. Laurell G, Borg E. Cis-platin ototoxicity in previously noise-exposed guinea pigs. Acta Otolaryngol (Stockh) 1980;101:66-74.

11. Farber BF, Maellering RC Jr. Retrospective study of the toxicity of preparations of vancomycin from 1974-1981. Antimicrob Agents Chemother 1983;23:138-41.

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STERNOMASTOID TUMOR OF INFANCY

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Sternomastoid tumor of infancy (SMTI) is the most common cause of neck mass in the perinatal period. We present seven children with this disorder, six studied prospectively. Ages at presentation ranged from 1 week to 4 weeks. Five had a history of birth trauma. Torticollis with facial asymmetry was seen in two. In six the diagnosis of SMTI was made clinically, and these patients were managed conservatively with massage and controlled stretching of the neck. Resolution of the neck mass, the torticollis, and the facial asymmetry occurred in all patients. Pathologic and radiographic findings are presented. We conclude that careful clinical assessment precludes the necessity of biopsy and emphasize the importance of conservative management of this transient problem.

KEY WORDS — congenital torticollis, fibromastosis coli, nodular fasciitis, sternomastoid tumor.

Sternomastoid tumor of infancy (SMTI) is a unique form of perinatal fibromatosis that results in the formation of a hard mass within the sternocleidomastoid (SCM) muscle of the neonate. Variously referred to as "fibromatosis coli" and "nodular fasciitis," SMTI is grouped within the spectrum of disorders collectively known as "congenital muscular torticollis" (CMT). This classification stems from a recognized relationship between SMTI and the variable development of torticollis in both infancy and later childhood. Although this association has clinical validity, it has focused attention primarily on CMT, despite the fact that SMTI is the most common cause of a neck mass in the perinatal period. In keeping with the emphasis on muscular torticollis, the majority of information pertaining to this group of disorders is found in orthopedic journals, with little emphasis in the otolaryngologic literature.

The purpose of this study was to evaluate our experience in neonates presenting with SMTI, emphasizing its transient nature, the importance of physical examination in the diagnosis, and the role of conservative management. We also would like to call attention among otolaryngologists to this disorder, in view of their expanding role in the care of problems of the head and neck.

MATERIAL AND METHODS

Seven infants with SMTI, seen and treated in the Division of Otolaryngology of Albany Medical College between 1983 and 1987, were included in this study (see Table). All patients underwent initial examination and follow-up by the senior author (P.J.K.). With the exception of the first case, all children were studied on a prospective basis. This included a careful physical examination that formed the basis of the diagnosis. All infants had a detailed birth history recorded. All children were reexamined at 1- or 2-month intervals until all signs and symptoms of their disease had resolved. The children were treated at home by the parents with massage of the involved SCM muscle with a topical ointment, as well as with controlled stretching of the neck on a twice-daily basis. The degree of mass size, torticollis, and facial asymmetry were noted on the initial and follow-up examinations. All seven patients were followed to complete resolution of their lesions.

RESULTS

The age of onset was between 7 and 28 days. All seven patients were male. Two patients had SMTI on the right. Four patients had SMTI on the left. One patient had bilateral SMTI. The neck masses ranged in size from 2 to 4 cm. Two of the seven patients (26%) presented with SMTI with torticollis. Both of these infants developed craniofacial asymmetry (plagiocephaly). Six of the seven patients (86%) had an associated history of birth trauma. All seven patients had complete resolution of their neck masses between 8 and 36 weeks of age. The two children with associated torticollis had complete resolution of this. Resolution of the facial asymmetry followed resolution of the torticollis in both cases.

CASE REPORTS

Case 1. A 5-week-old boy was referred to our clinic by his pediatrician for evaluation of bilateral neck masses. These had been noted shortly after the child's uneventful birth, by his aunt, a family practitioner. An extensive workup was performed on the child prior to the referral and included cervical radiographs and computed tomography, as well as catecholamine studies to rule out neuroblastoma.

Examination revealed a healthy child with bilateral 3- to 4-cm nontender, hard, lobulated masses at

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SEVEN CASES OF STERNOMASTOID TUMOR OF INFANCY

Case	*Sex*	*Age at Onset (wk)*	*Side*	*Size*	*Birth History*	*Torticollis*	*Plagiocephaly*	*Age at Resolution of Tumor (wk)*	*Resolution of Torticollis and Plagiocephaly*
1	M	2	Bilateral	3-4 cm	Normal vaginal, primiparous	–	–	13	Not applicable
2	M	3	R	2 cm	Breech vaginal	–	–	16	Not applicable
3	M	2	L	2 cm	Breech presentation, C-section	+	+	14	Torticollis 7 mo, plagiocephaly 12 mo
4	M	2	L	3 cm	Normal vaginal	–	–	36	Not applicable
5	M	4	R	3 cm	Forceps vaginal, primiparous	+	+	28	Torticollis 7 mo, plagiocephaly 13 mo
6	M	4	L	4 cm	Breech forceps vaginal	–	–	16	Not applicable
7	M	1	L	2 cm	Difficult, with birth weight of 4 kg (9 lb)	–	–	8	Not applicable

the distal ends of both SCM muscles. These were poorly delineated by the plain cervical radiographs (Fig 1A). The CT (Fig 1B) revealed discrete solid masses within the body of the SCM muscle bilaterally. A diagnostic ultrasound scan (Fig 1C) showed bilateral solid masses superficial to the great vessels of the neck. An open biopsy of the mass was performed for diagnosis. Findings at surgery revealed a fibrous mass in the distal end of the left SCM muscle that was white and chalky in appearance. The histopathology revealed diffuse fibrosis that the pathologist called "nodular fasciitis consistent with fibromatosis coli" (Fig 1D).

Once the diagnosis was made, the child was started on a regimen of physical therapy that included twice-daily massage of the lower ends of the SCM muscles as well as passive stretching of the neck. Both masses resolved within 6 weeks of the biopsy.

This was the first case in our series and prompted a search of the literature regarding the problem of SMTI and CMT. Based on the knowledge gained from this case, as well as the information available from the literature, our study was established to evaluate the role of history and physical examination in the diagnosis of SMTI, along with the value of conservative management for the therapy of these lesions.

Case 3. A 16-day-old boy was referred to our clinic by our pediatric oncology colleagues for evaluation of the acute onset of a mass in his left neck (Fig 2). He had been delivered by cesarean section following a difficult breech presentation.

Examination revealed a nontender rock-hard mass in the middle third of the left SCM muscle, mobile in the horizontal direction. The child's head was noticeably tilted to the left. A diagnosis of SMTI with torticollis was made, and physical therapy was begun with twice-daily neck massage and passive stretching of the neck. On his monthly follow-up visit, craniofacial flattening also was noted.

Within 3 months the SMTI resolved. At the age of 7 months the torticollis resolved. At 1-year follow-up the child had full range of motion of his neck with no evidence of facial asymmetry.

DISCUSSION

The dramatic deformity of "wry neck" has been recognized since antiquity and has been a recurring historical theme of medical interest since Plutarch's description of Alexander the Great's neck deformity, interpreted by some as a case of torticollis.[1] Defined as a contracture of the SCM muscle that produces a head tilt toward the involved side with subsequent neck torsion and facial deviation, torticollis is the physical end point of a variety of different disorders. Although there are neurologic and inflammatory causes of torticollis, the most frequent type results from a congenital idiopathic fibrosis within the SCM muscle of neonates and has been most consistently termed CMT.

In 1826 Hensinger first described a congenital fibrous tumor in the SCM muscle of neonates that has since come to be known as SMTI.[2] Subsequent authors[3-7] have recognized it as a unique clinical entity variably associated with the development of torticollis. Histologically, the pictures of SMTI and CMT are identical, and thus much of the relevant information on SMTI has been grouped with CMT in the medical literature. This has led to some confusion in the nomenclature of these related disorders, and terms such as congenital muscular torticollis, muscular torticollis, sternomastoid torticollis, fibromatosis coli, nodular fasciitis, sternomastoid fibrosis, and sternomastoid tumor of infancy are used interchangeably. We agree with authors[5,6] who advocate the term SMTI when a mass is palpable and "muscular torticollis" when only contracture of the SCM muscle is present.

Generally, SMTI presents as a firm, nontender spindle-shaped nodule in the distal third of the SCM muscle in the neonate (Fig 2). The age of onset is between 7 and 28 days, and there is usually an equal sex ratio. The predominance of males in our series is

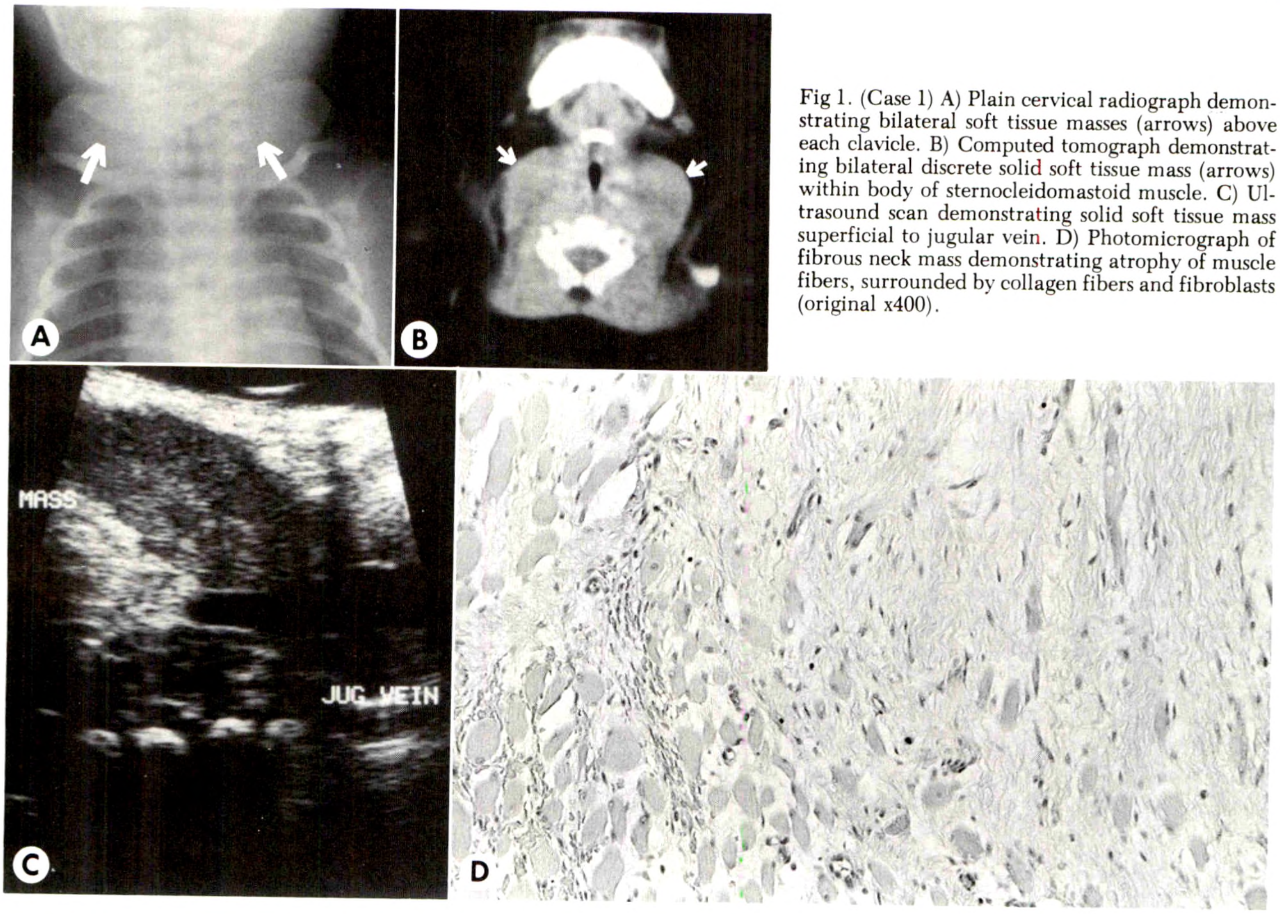

Fig 1. (Case 1) A) Plain cervical radiograph demonstrating bilateral soft tissue masses (arrows) above each clavicle. B) Computed tomograph demonstrating bilateral discrete solid soft tissue mass (arrows) within body of sternocleidomastoid muscle. C) Ultrasound scan demonstrating solid soft tissue mass superficial to jugular vein. D) Photomicrograph of fibrous neck mass demonstrating atrophy of muscle fibers, surrounded by collagen fibers and fibroblasts (original x400).

a reflection of our small sample size. Although there is some variability, many series report a higher incidence of SMTI on the right side. There is no obvious reason why the right side should be more frequently involved than the left, and indeed, when the results of four large series[5-8] are totaled (250 on the right, 224 on the left) the difference is not statistically different. Bilaterality has been reported, but is considered rare, with an incidence of 2% to 3%.[9]

The natural history of both SMTI and muscular torticollis has been studied thoroughly. In a prospective review of 100 children, Jones[9] found that 66% had SMTI and 34% had muscular torticollis without tumor. In half the infants with SMTI the muscle was normal by the age of 6 months, while in 30% there was palpable fibrosis without contracture. In 9% the tumor persisted with resultant torticollis. Coventry and Harris,[7] in a retrospective study of 35 cases at the Mayo Clinic, found that SMTI disappeared at the average age of 14 weeks, with complete resolution in 30 of 35 cases (86%). Ling and Low,[5] in a retrospective review of 84 cases of SMTI, reported complete resolution in 77% of patients at the average age of 7 months, while 23% of cases progressed to torticollis. MacDonald[6] reviewed his personal experience with 50 infants with SMTI between 1950 and 1965 in Bristol, England. This series is notable for its prolonged follow-up, with two thirds followed an average of 6 years. A quarter of the patients had transient torticollis that subsided with the tumor. Forty-three (86%) resolved their tumor entirely, but of these patients, 25% had minor but detectable asymmetry or tightness of the SCM muscle. Seven (14%) subsequently developed torticollis. It is apparent that SMTI is a transient phenomenon that can be associated with both temporary and permanent torticollis. The factors that predispose a child toward long-term deformity are not obvious, since the evolution and resolution of these lesions is highly unpredictable.

The variable natural history of SMTI may well be related to its underlying pathophysiology, about which there is little agreement. Numerous theories have been proposed; however, it is questionable

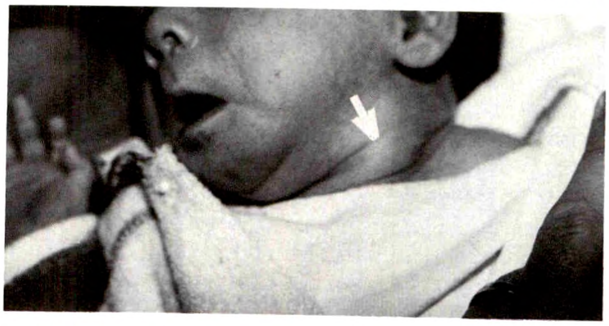

Fig 2. (Case 3) Sixteen-day-old infant with tumor of middle third of left sternocleidomastoid muscle.

whether there is a single etiologic process responsible for the formation of these tumors. Both SMTI and muscular torticollis present with the deposition of fibroblasts and collagen around atrophying muscle fibers (Fig 1D). The extent and density of the muscle replacement varies, but it is generally more widespread than what would be expected of a localized tumor.[9]

The association between SMTI and breech, forceps, and primiparous births has been long recognized, and not surprisingly, difficult delivery has been implicated in the development of these lesions. As early as 1838, Stromeyer proposed that rupture of the SCM muscle with hematoma formation due to traumatic birth resulted in the fibrosis of the muscle.[1] Subsequent studies, however, have failed to demonstrate significant hemosiderin deposits indicating hemorrhage.[1] Other observations, such as SMTI following cesarean section,[4,6] the presence of mature fibrosis in the newborn's neck,[9] and the association of SMTI with other congenital lesions such as hip dysplasia,[4,8] suggest that the development of SMTI is at least in some cases an intrauterine phenomenon. These have led some to speculate that it is prenatal fibrosis that is responsible for the difficult delivery, rather than the other way around.[7,9]

Middleton,[3] in 1930, was able to produce experimental muscle fibrosis by venous ligation of the sartorious muscle in the dog, and he proposed that venous obstruction during birth was the cause of SCM muscle injury. This interpretation has been challenged by others,[4] who point out that venous obstruction during delivery is generally of insufficient duration to produce SCM muscle vascular stasis and subsequent fibrosis. Nevertheless, the demonstration that venous obstruction leads to muscle fibrosis is most consistent with the clinical picture of SMTI and can be valid without the assumption that it is caused by traumatic delivery. It seems plausible that muscular venous obstruction can be due to intrauterine positioning as well as obstetric difficulties, and the variable timing of the obstruction can explain the conflicting observations regarding the pathophysiology of SMTI.

The occurrence of SMTI is worldwide, and its incidence is remarkably high. Coventry and Harris[7] calculated an incidence of four per 1,000 births in Minnesota. Ling and Low[5] report an incidence of five per 10,000 births in Singapore. Assuming the more conservative estimate, no other cause of neck mass in the immediate perinatal period approaches such a high incidence. Moreover, the frequency of this disorder suggests that many otolaryngologists in their capacity as head and neck specialists will be called upon to diagnose SMTI.

It has been stated that "the diagnosis of congenital muscular torticollis in infancy should be readily made by any informed physician."[7] Nevertheless, the presence of a hard, minimally mobile neck mass in a newborn infant in our cancer-conscious age can be a source of great anxiety for both parents and physicians. Indeed, two of our patients were referred to us by our pediatric oncology colleagues. Although Gruhn and Hurwitt,[10] in their extensive literature review, have pointed out that there has never been a recorded case of a malignancy in the SCM muscle of a neonate, SMTI presents the clinician with the problem of differentiating this benign and transient problem from other, more aggressive neoplastic processes such as neuroblastoma, rhabdomyosarcoma, and fibrosarcoma.

As an aid to diagnosis we found imaging of variable value. The plain cervical radiograph (Fig 1A) in one case was normal and in another poorly delineated the SMTI. The CT scan (Fig 1B) on one child with bilateral SMTI revealed discrete solid masses within the bodies of both SCM muscles. Ultrasound (Fig 1C) in two cases consistently showed solid masses superficial to the great vessels of the carotid sheath. While imaging did not provide a definitive diagnosis, both CT and ultrasound accurately localized the disease to the SCM muscle, thus confirming the findings of the physical examination.

Although there is an extensive differential diagnosis of neck masses in children,[11] we know of no other entity that presents so soon after birth, with such anatomic specificity, and with the physical characteristics of SMTI. From our experience as well as from our review of the literature, we concur with other authors[1,7,10,12] that the diagnosis of SMTI can be based relatively safely on knowledge of its natural history and clinical presentation. Biopsy should be reserved for cases in which there is uncertainty in the diagnosis or in which the lesion fails to resolve spontaneously.

Surgical correction of torticollis by tenomyotomy has been practiced for two millennia.[1] However, the traditional treatment of SMTI has been observation in conjunction with conservative measures of massage and passive stretching of the neck, on the basis of the finding that 80% of these lesions spontaneously regress.[6,7,10] Some surgeons familiar with the long-term problems in the remaining 20%, such as torticollis and facial asymmetry, have favored early excision of SMTI.[4] However, it remains to be shown that prophylactic excision will prevent fixed skeletal deformities from occurring. Based on the available evidence, we believe that the early management of SMTI should be observation. The value of conservative manipulation of the involved muscle has never been studied objectively, but is conceptually appealing. From our observation, massage with an emollient cream and passive gentle stretching provides the parents a valuable opportunity to participate actively in the care of their infant and contributes to parental bonding in this formative period, and we highly recommend these simple measures.

In summary, SMTI is a unique form of fibrosis of the SCM muscle of newborns and is the most common cause of neck mass in the perinatal period. It presents as a hard, nontender mass in the distal third of the infant's SCM muscle, generally between 1 and 4 weeks of age. It can be associated variably with birth trauma; however, whether it is the cause or the result of this trauma remains to be proved. It is associated variably with muscular torticollis and craniofacial asymmetry, and although these resolve in the majority of cases, a small percentage of patients will develop fixed deformities. The diagnosis of this benign disorder is based on its clinical recognition and should be managed with simple physiotherapy and observation.

REFERENCES

1. McDaniel A, Hirsch BE, Kornblutt AD, Armbrustmacher VM. Torticollis in infancy and adolescence. Ear Nose Throat J 1984;63:478-87.
2. Hansen DA. Torticollis. S Afr Med J 1972;46:480-2.
3. Middleton DS. The pathology of congenital torticollis. Br J Surg 1930;18:188-204.
4. Chandler FA, Altenberg A. Congenital muscular torticollis. JAMA 1944;125:476-83.
5. Ling CM, Low YS. Sternomastoid tumor and muscular torticollis. Clin Orthop 1972;86:144-50.
6. MacDonald D. Sternomastoid tumor and muscular torticollis. J Bone Joint Surg 1969;51:432-43.
7. Coventry MB, Harris LE. Congenital muscular torticollis in infancy. J Bone Joint Surg 1959;41:815-22.
8. Binder H, Eng GD, Gaiser JF, Kock B. Congenital muscular torticollis. Arch Phys Med Rehabil 1987;68:222-5.
9. Jones PG. Torticollis. In: Jones PG, Mustard WT, eds. Pediatric surgery. Chicago: Yearbook Medical Publishers, 1969: 293-8.
10. Gruhn J, Hurwitt ES. Fibrous sternomastoid tumors of infancy. Pediatrics 1951;8:522-6.
11. May M. Neck masses in children. Ear Nose Throat J 1978;57:136-59.
12. McQueen WJ, Johnson JT, Edwards PA. Fibromatosis colli: a case report. Otolaryngol Head Neck Surg 1980;88:49-51.

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The University of Iowa Department of Otolaryngology–Head and Neck Surgery and the International Cochlear Implant Association will hold the Second International Cochlear Implant Symposium in Iowa City on June 4-9, 1990. The symposium will focus on basic science aspects of electrical stimulation on the auditory system, new cochlear implant strategies, clinical application in both adults and children, and rehabilitation and educational issues. Please submit abstracts to Bruce J. Gantz, MD, Department of Otolaryngology–Head and Neck Surgery, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

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DURATION AND FREQUENCY CHARACTERISTICS OF TRACHEOESOPHAGEAL SPEECH

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Selected characteristics were compared in the speech of five tracheoesophageal, five esophageal, and 15 normal laryngeal adult speakers. Tape-recorded speech samples were measured for durational features with a stopwatch. Frequency features were analyzed with a Visi-Pitch/Apple IIE computer interface with statistical subroutines. Tracheoesophageal speech proved comparable to normal speech in maximum phonation time, speech rate, pitch pertubation (jitter), average fundamental frequency, and fundamental frequency range, but less efficient than normal speech in phrase grouping. Tracheoesophageal speech was superior to esophageal speech in maximum phonation time, speech rate, and phrase grouping, but not significantly different in pitch perturbation, average fundamental frequency, and fundamental frequency range. Explanations and clinical implications of these findings are discussed.

KEY WORDS — esophageal speech, laryngectomee, speech therapy, tracheoesophageal speech.

INTRODUCTION

The tracheoesophageal (T-E) puncture technique for laryngectomees has become a popular medical procedure over the past decade. This popularity may be attributed to its surgical simplicity and the practical benefits afforded the patient. These include a decreased danger of aspiration, the use of pulmonary-supported air for speech, and a rapid recovery of speech in lieu of a lengthy, traditional vocal rehabilitation program.

While much research has compared acoustic characteristics of esophageal and artificial larynx speech, little has been written on T-E speech characteristics apart from a single investigation.[1-4] Esophageal speakers are able to phonate over a wide range of discrete frequencies,[5,6] yet it is not known conclusively[7] to what extent they use pitch variability in connected speech. Such information on the dynamic control of frequency in T-E speech also is warranted. Gandour and Weinberg[8] have shown that esophageal and T-E speakers are perceived by listeners to achieve intonational contrasts. It is desirable, both clinically and scientifically, to know objective acoustic measures that may relate to perceived characteristics of alaryngeal speech. The present study, then, analyzed certain duration and frequency features of T-E speech to independently add to existing data[1-4]; yet subjects in the present study used the newer low resistance devices available on the market today. Measures also were made on esophageal and normal laryngeal speech for comparison purposes.

METHODS

Tracheoesophageal, esophageal, and normal laryngeal forms of speech were compared on six measures: maximum phonation time, speech rate, phrase grouping, relative average perturbation, average fundamental frequency, and fundamental frequency range. Subjects were volunteers from area clubs sanctioned by the International Association of Laryngectomees. The five T-E, five esophageal, and 15 normal speakers ranged in age from 50 to 75; subjects were matched for age (within 5 years) and balanced for sex (one of every five was female). Table 1 summarizes background information of alaryngeal subjects regarding sex, age, level of education, time elapsed since laryngectomy, and history of alaryngeal speech treatment. All T-E subjects wore the Blom-Singer T-E prosthesis, and four of the five also used a tracheostoma valve. Subjects were individually tape-recorded (Tascam 22-2 reel-to-reel) while performing a standard order of tasks. Speech samples included maximum prolongation of the vowel /a/ (two trials given), reading aloud a monosyllabic word list (50 words selected from the Black and Haggen Tests of Intelligibility[9]), reading aloud the 98-word Rainbow Passage, and conversing with the investigator about employment and/or hobbies.

Three durational measures were of interest. The two recorded attempts to maximally prolong the vowel /a/ were measured with a digital, sprint-style stopwatch (Delta Impex, 1052p). The trial with the longest duration was taken as the subject's maximum phonation time, a measure that infers adequacy of air support for speech. The time needed to read the prose passage was measured with a stopwatch; speech rate was extrapolated as words read per minute (wpm). Breaths or air charges were marked by listening and observing as each subject read aloud. The number of words per breath or charge were counted and then averaged for each speaker; this measure was termed phrase grouping.

Three frequency measures were of interest. The second sentence of the passage was analyzed to find

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TABLE 1. BACKGROUND INFORMATION ON ALARYNGEAL SUBJECTS

Subject	*Sex*	*Age*	*Education*	*Time Since Laryngectomy (yr)*	*Treatment History*
Tracheoesophageal*					
T-1	M	61	High school	1.9	None
T-2	M	60	PhD	2.8	None
T-3	F	52	Some college	10.3	Negligible
T-4	M	62	High school	11.1	None
T-5	M	66	High school	3.6	Negligible
Esophageal					
E-1	M	72	High school	5.0	1 yr
E-2	M	70	High school	13.0	1 yr
E-3	F	70	College	1.4	9 mo
E-4	M	75	College	17.7	3 mo
E-5	M	53	High school	1.2	3 mo

*Blom-Singer prosthesis.

the average fundamental frequency of the glottis or pseudoglottis. A Visi-Pitch/Apple IIE computer interface (Kay Elemetrics, 6096) with statistical subroutines performed this frequency analysis. In this program, average fundamental frequency is calculated from the number of glottal pulses per unit time. Pitch variability, or fundamental frequency range, was determined from the same sample by use of the Visi-Pitch system. The range represents the fundamental minimal-maximal difference. Jitter, the cycle-to-cycle variation in fundamental frequency, was analyzed with the Visi-Pitch subroutine by use of Koike's formula.[10] These values of relative average pitch perturbation were extracted from the midpoint of the sustained vowel to minimize effects of voice initiation and termination. The vowel /a/ was used because of its sensitivity for jitter.[11]

RESULTS

Subject data are summarized in Table 2. The one-way, completely randomized analysis of variance was used for each comparison across the three groups of subjects. Interjudge reliabilities were established for the noncomputerized duration measures and found to be between 87% and 100% for all speakers prolonging the vowels, 96% to 100% for speech rate, and 79% to 100% for the phrase grouping measure. When agreement between the two judges was less than 100%, the mean of the two measures was used for further analyses.

TABLE 2. DATA FROM INDIVIDUAL SUBJECTS FOR STUDY MEASURES

Subject	*Duration of /a/ (s)*	*Speech Rate (wpm)*	*Phrase Grouping (No. of Words)*	*Perturbation of /a/ (%)*	*Fundamental Frequency (Hz)*	*Frequency Range (Hz)*
Tracheoesophageal						
T-1	21.64	176.5	8.00	5.12	136.6	151.3
T-2	15.51	163.3	9.80	5.79	73.5	154.0
T-3*	8.27	134.2	8.10	9.63	158.4	302.7
T-4	12.57	137.1	7.90	1.60	88.4	101.0
T-5†	23.75	150.0	6.70	0.83	81.8	139.0
Average	16.35	152.2	8.10	4.59	107.7	169.6
Esophageal						
E-1	2.32	107.6	4.00	7.56	89.7	118.6
E-2	2.64	77.9	4.50	10.97	81.2	152.1
E-3*	1.44	77.9	2.40	4.04	100.0	251.5
E-4	1.66	132.0	3.30	4.53	80.4	153.6
E-5	1.08	73.5	3.60	11.13	69.1	209.5
Average	1.83	93.8	3.56	7.65	84.1	177.1
Normal						
N-1	19.20	184.0	15.10	2.15	92.0	81.0
N-2	26.62	155.0	10.80	2.38	106.0	111.0
N-3*	27.59	120.0	13.40	3.35	174.0	213.0
N-4	38.36	147.0	10.80	2.39	101.0	95.0
N-5	27.89	125.0	12.00	3.48	127.0	133.0
N-6	29.00	178.0	11.80	1.10	118.0	116.0
N-7	20.92	151.0	12.50	1.11	113.0	109.0
N-8*	22.60	168.0	10.90	0.77	204.0	167.0
N-9	28.18	143.0	14.00	0.47	109.0	122.0
N-10	19.85	173.0	10.00	3.39	104.0	93.0
N-11	20.30	173.0	11.20	1.19	102.0	83.0
N-12	21.44	118.0	13.70	0.37	121.0	161.0
N-13*	24.40	168.0	12.20	0.37	229.0	155.0
N-14	16.66	189.5	13.10	4.34	120.4	149.5
N-15	30.53	189.8	11.00	1.34	106.1	143.8
Average	24.90	158.8	12.17	2.03	128.4	128.8

wpm — words per minute.
*Female subjects.
†Subject without tracheostoma valve.

Maximum Phonation Time. The maximum duration with which the vowel /a/ could be sustained differed significantly among esophageal, T-E, and normal subjects ($F = 36.89$, $p < .01$). Normal speakers averaged a maximum duration of 24.90 seconds ($SD = 5.4$), whereas T-E speakers averaged 16.35 ($SD = 5.71$), and esophageal speakers only 1.83 seconds ($SD = 0.57$). Post hoc testing using the Newman Keuls procedure showed that normal speakers were able to prolong the vowel /a/ significantly longer than esophageal speakers ($p < .01$). The T-E speakers also were significantly better at extending phonation than esophageal speakers ($p < .01$); T-E and normal speakers were not significantly different ($p > .05$).

Speech Rate. A significant difference was found in rate of speaking, during reading, of the three groups ($F = 14.79$, $p < .01$). Normal speakers ($\bar{x} = 158.8$ wpm, $SD = 23.5$) averaged six wpm faster than T-E speakers ($\bar{x} = 152.2$ wpm, $SD = 15.9$); this difference, however, was not significant ($p > .05$). Normal speakers were more than 65 wpm faster than esophageal speakers ($\bar{x} = 93.8$ wpm, $SD = 22.7$), and this difference was significant ($p < .01$). The T-E speakers were significantly faster ($p < .01$) than the esophageal speakers, and this rate difference was in excess of 58 wpm.

Phrase Grouping. A significant difference was found among the three groups for number of words spoken per breath or charge of air ($F = 87.64$, $p < .01$). Post hoc testing revealed that all three groups were significantly different from each other ($p < .01$). The T-E speakers ($\bar{x} = 8.10$; $SD = 0.99$) averaged nearly five words per breath more than the esophageal speakers ($\bar{x} = 3.56$, $SD = 0.71$); this difference was even greater for the normal speakers ($\bar{x} = 12.17$, $SD = 1.39$), who averaged nearly nine words more than their esophageal counterparts. Normal speakers were superior to T-E speakers by more than four words per breath.

Relative Average Perturbation. A significant difference was found among the three groups for relative average perturbation of /a/ ($F = 11.32$, $p < .01$). Post hoc testing revealed significant differences only between normal and esophageal speakers ($p < .01$). Average perturbations of /a/ for the normal group ($\bar{x} = 2.03\%$, $SD = 1.27$) were not significantly less than perturbations in the T-E group ($\bar{x} = 4.59\%$, $SD = 3.17$, $p > .05$). Likewise, the T-E group did not display significantly less jitter than the esophageal group ($\bar{x} = 7.65\%$, $SD = 3.03$, $p > .05$). Both T-E and esophageal groups exhibited large variability of pseudoglottal jitter.

Average Fundamental Frequency. No significant differences were found in the average fundamental frequencies of the three speaker groups at the .05 level. The fundamental frequency of normal speakers ($\bar{x} = 128.4$ Hz, $SD = 39.3$) was slightly higher than that of the T-E speakers ($\bar{x} = 107.7$ Hz, $SD = 33.5$). Both normal and T-E speakers displayed great variability in this measure; in particular, the data of two T-E subjects skew the average toward the high end. Esophageal speech averaged the lowest frequency level ($\bar{x} = 84.1$ Hz, $SD = 10.3$), although it was not significantly lower than the other groups.

Fundamental Frequency Range. The ranges of vocal fundamental frequency used during connected speech were not significantly different among the three groups. The similarity of these ranges is evident, with normal speakers averaging 128.8 Hz ($SD = 35.3$), T-E speakers 169.6 Hz ($SD = 69.2$), and esophageal speakers 177.1 Hz ($SD = 47.3$).

DISCUSSION

Data on maximum phonation time of the vowel show that normal speakers could prolong phonation in excess of 24 seconds, T-E speakers about 16 seconds, and esophageal speakers less than 2 seconds. These results compare closely with the 22-, 12-, and 2-second values reported by Robbins et al[1-4] for normal, T-E, and esophageal speakers, respectively. However, others[5,6,12] found longer vowel duration times, on the order of 5 to 6 seconds, for esophageal speakers. Proficiency of esophageal speakers in various studies may account for these discrepancies. That T-E speakers and normal speakers obtained longer vowel duration times than esophageal speakers is not surprising because of their pulmonary air utilization. However, the magnitude of difference between the normal and T-E speakers is of interest, since both are pulmonary-supported speech forms. The resistance provided by the puncture prosthesis can account only partly for this difference. Further decrements in air expenditure may be explained by the usage of a Singer-Blom tracheostoma valve by the majority of T-E speakers in this study. The tracheostoma valve may create an even greater resistance than the prosthesis alone, causing the T-E speakers to expend more air. This results in pulmonary air being depleted quicker, and thus phonation can be prolonged for a shorter period of time.

The normal group and the T-E group demonstrated a significantly faster speech rate, 159 and 152 wpm, respectively, than did esophageal speakers at 94 wpm. These results agree quite well with those of previous research.[1,3-5] Both normal and T-E speakers utilize pulmonary air for speech. It therefore is logical that speech rates would not differ significantly, and this was found to be the case in the present data. As for esophageal speakers, their rate inefficiency can be attributed to the increased pause time needed to insufflate the pseudoglottis.

Phrase grouping results found the normal and

T-E speakers to have significantly more words per breath than the esophageal speakers. This may be explained by the utilization of pulmonary air in both normal and T-E speech. The amount of air that can be injected and momentarily stored in the esophagus is considerably less than the amount taken into the lungs and airway by normal and T-E speakers. Hence, esophageal speakers have less air on which to speak, so they must pause more frequently to replenish speech air. A significant difference also was found between normal and T-E speakers, despite the use of pulmonary air by both. Perhaps this difference of about four words per breath can be explained three ways. First, the prosthesis worn in the T-E site provides airway resistance greater than that found in normal voice tracts.[13] This is true no matter what model or brand of device is worn. A second source of airway resistance comes from the use of a tracheostoma valve, which most subjects wore. Additionally, it may be posited that as valves age, their plastic becomes brittle and further increases resistance during speech. Such increased resistance may cause T-E speakers to use more effort, possibly even more air, to get their speech out. This would allow for fewer words per breath.

Regarding phrase grouping, the present data compare favorably with values cited in the literature. The average for the normal speakers of 12.17 words per breath was similar to Snidecor and Curry's[5] result of 12.5 words per breath for normal speakers, but was higher than the 9.8 words per breath found by Robbins et al.[2,4] Snidecor and Curry[5] found a range of 2.8 to 6.3 words per charge for esophageal speakers, and Robbins et al[2,4] found esophageal speakers to have an average of 3.0 words per charge. The average of 3.56 words per charge found in the present study agrees well. The number of words spoken per breath of air by the T-E subjects averaged 8.10, which is similar to the 7.2 words per breath cited in the literature.[2,4]

Results of the relative average perturbation data on /a/ were surprising in that only esophageal speech differed significantly from normal speech. Previous investigations[1,2,4] show large differences in perturbation among all three groups of speakers, yet different methods of analysis and expressions of jitter were used. As stated by Horii,[14] special caution is necessary in comparing data or performance values from various analysis methods. Steinsapir et al[15] demonstrated that different instruments (such as the Visi-Pitch and the PM300 Pitch Analyzer) generate different jitter values even when measuring the same sample. More importantly for this investigation, they demonstrated high intrajudge and interjudge reliability when using taped samples with the Visi-Pitch.

No difference was found in fundamental frequency among the three groups of speakers. Average fundamental frequencies of previously reported esophageal data are close to the average fundamental frequency of esophageal speakers found in this study. Specifically, the present average of 84 Hz is in perfect agreement with Shipp[12] and only slightly higher than the 72 to 77 Hz reported by others.[1-4,7] The T-E speakers in this study had an average fundamental frequency of 108 Hz, which compares favorably with the fundamental frequency of T-E speakers cited in the literature, especially the 102 Hz reported by Robbins et al.[1-4] The fundamental frequency of normal speakers at 128 Hz is comparable with that from other research.[16]

Although no significant differences were found among the three groups for fundamental frequency range during connected speech, the normal speakers averaged the smallest frequency range, 129 Hz. The T-E speakers had a group average range of 170 Hz. However, as seen in Table 2, the majority of T-E speakers had individual ranges of 150 Hz or less. One speaker (who exhibited some diplophonia, in the opinion of the investigator) had a range of 303 Hz, which brought the group average up considerably. The esophageal speakers also had an average range of 177 Hz, which was higher than expected. Although the topic has not been frequently studied, Filter and Hyman[7] report pitch variability of esophageal speech to be about 80 Hz. The present finding of no significant differences among the three groups lends support to the findings of Gandour and Weinberg.[8] Frequency variability probably was produced equally well by normal, esophageal, and T-E speakers, since listeners perceived intonational contrasts effectively in all three groups.

CONCLUSIONS

The duration and frequency characteristics of alaryngeal speech found in this study lend credence to data previously published. Responsible patient counseling by laryngologists and speech pathologists should include a discussion of speech characteristics. Both patients and speech pathologists can use such normative data in setting rehabilitation goals and in comparing a patient's speech to that of peers. Deficit areas may be identified and practiced more strenuously in therapy. By shaping of such speech characteristics, listeners' perceptions may be affected.[8]

The specific duration and frequency characteristics measured in this study, on a limited number of subjects, yield the following statements. Tracheoesophageal speakers prolong phonation an average of about 16 seconds, ie, not as long as normal speakers but significantly longer than the 2 seconds of most esophageal speakers. Tracheoesophageal speakers, because they use pulmonary air, can talk at rates comparable to normal. Esophageal speakers' rates average a slower 94 wpm because of the time involved in insufflating the pseudoglottis. This same air charge is sufficient for only three to four words. Tracheoesophageal speakers, using lung air, can say about eight words per breath, or four words fewer than normal. This decrement is probably due to the resistance of the prosthetic device(s). Esophageal speech exhibits significantly more jitter than normal speech. Tracheoesophageal speech exhibits pitch perturbation values between those of esophageal and normal speech, making it not significantly different from either speech method. The measures of average fundamental frequency and fundamental frequency range were comparable between normal, T-E, and esophageal speakers. This suggests that alaryngeal speakers can attain frequency parameters not too unlike those of normal speech. These findings are supported in some of the literature, yet warrant further acoustic and perceptual verification.

REFERENCES

1. Robbins J, Fisher HB, Logemann J, Hillenbrand J, Blom E. A comparative acoustic analysis of laryngeal speech, esophageal speech, and speech production after tracheoesophageal puncture. Presented at the meeting of the American Speech-Language-Hearing Association, Los Angeles, Nov 20-23, 1981.

2. Robbins J. Acoustic differentiation of laryngeal, esophageal, and tracheoesophageal speech. J Speech Hear Res 1984;27:577-85.

3. Robbins J, Fisher H, Blom EC, Singer MI. Selected acoustic features of tracheoesophageal, esophageal, and laryngeal speech. Arch Otolaryngol 1984;110:670-2.

4. Robbins J, Fisher H, Blom EC, Singer MI. A comparative acoustic study of normal, esophageal, and tracheoesophageal speech production. J Speech Hear Disord 1984;49:202-10.

5. Snidecor JC, Curry ET. How effectively can the laryngectomee expect to speak? Laryngoscope 1960;70:62-7.

6. Weinberg B, Bennett S. Selected acoustic characteristics of esophageal speech produced by female laryngectomees. J Speech Hear Res 1972;15:211-6.

7. Filter MD, Hyman M. Relationship of acoustic parameters and perceptual ratings of esophageal speech. Percept Mot Skills 1975;40:63-8.

8. Gandour J, Weinberg B. Perception of intonational contrasts in alaryngeal speech. J Speech Hear Res 1983;26:142-8.

9. Black JW, Haggen CH. Multiple-choice intelligibility tests, forms A and B. J Speech Hear Disord 1963;28:77-86.

10. Koike Y. Application of some acoustic measures for the evaluation of laryngeal dysfunction. Stud Phonolog 1973;7:17-23.

11. Horii Y. Vocal shimmer in sustained phonation. J Speech Hear Res 1980;23:202-9.

12. Shipp T. Frequency, duration, and perceptual measures in relation to judgments of alaryngeal speech acceptability. J Speech Hear Res 1967;10:417-27.

13. Costello J. Speech disorders in adults. San Diego: College-Hill Press, 1985.

14. Horii Y. Jitter and shimmer differences among sustained vowel phonations. J Speech Hear Res 1982;25:12-4.

15. Steinsapir CD, Forner LL, Stemple JC. Comparison of data from the Visi-Pitch and the PM300 Pitch Analyzer. Presented at the meeting of the American Speech-Language-Hearing Association, Detroit, Nov 21-24, 1986.

16. Fitch J, Holbrook A. Modal vocal fundamental frequency of young adults. Arch Otolaryngol 1970;92:379-82.

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SURGICAL IMPLANTATION AND BIOCOMPATIBILITY OF CENTRAL NERVOUS SYSTEM AUDITORY PROSTHESES

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As part of a program to determine the feasibility of a CNS auditory prosthesis, the tissue reaction to electrodes chronically implanted in the cochlear nucleus (CN) of the guinea pig was examined. Varied open operative approaches and microelectrode designs were utilized. Silicon substrate thin film and platinum-iridium wire electrodes, tethered and untethered, were placed successfully in different divisions of the CN. Implantation through a posterior suboccipital approach was most successful. Histologic examinations demonstrated a glial cell proliferation confined to the area of the electrode track that never exceeded 15 μm in width. No neuronal loss or significant effect on cell morphology was seen, and reactive cells were absent. Electrode migration was apparent in a minority of animal preparations. Although potential problems were identified, our findings lend support to the feasibility of implanting a neuroprosthesis in the CN and have helped to establish methods for future studies of chronic intranuclear stimulation.

KEY WORDS — auditory prosthesis, chronic implantation, cochlear nucleus, implant.

INTRODUCTION

Applications of neuroprosthetic stimulation for rehabilitation of the profoundly deaf have undergone considerable development over the past two decades. Cochlear implantation continues to gain acceptance as a means of facilitating environmental and speech sound processing. Successful use of a standard cochlear implant requires the presence of at least some viable auditory nerve fibers, as well as an intact cochlea with an implantable scala tympani. This approach is often not applicable to deafened individuals who lack these components of the peripheral auditory system. This may result from bilateral surgical ablation of the auditory nerves for tumor removal or from otic capsule dysgenesis.

Clinical observations at the House Ear Institute[1-4] have suggested that prosthetic stimulation of the cochlear nucleus (CN) surface is capable of producing auditory sensations. The present animal study examines the feasibility and safety of implanting the CN with a penetrating electrode. Theoretically, a penetrating electrode with multiple stimulation sites could selectively activate spatially separated neurons. This would provide the potential for differential stimulation of neuronal subpopulations providing pitch discrimination.

Penetrating microelectrodes of two designs were examined in the guinea pig model. One of these designs permitted monitoring electrophysiologic responses intraoperatively in order to determine the accuracy of microelectrode placement. Operative exposure of the CN and animal tolerance of CN implantation were tested by use of transbullar (TB) and suboccipital (SO) approaches. Histologic assessment was performed to determine tissue tolerance of untethered and lead-tethered electrodes in the CN region of the pontomedullary brain stem.

METHODS

Electrodes. Biocompatibility of microelectrodes of two designs was tested in 18 animal preparations.

1. Multichannel probes with five contacts were fabricated from a micromachined silicon substrate (Fig 1A). This substrate supports an array of thin-film polysilicon conductors that are insulated above and below by deposited silicon-oxide and silicon-nitride layers. Conductors at the stimulating sites and bond pad areas remain exposed. Untethered (n = 6) and lead-tethered (n = 6) Si probes were implanted. Tethered Si probes were anchored to the skull surface with a connecting flexible lead made of 2.54-μm platinum–10% iridium (Pt–10% Ir) alloy Teflon-coated wire.

2. Single-channel bipolar microelectrodes were fabricated with 7.62-μm Pt–10% Ir Teflon-coated wire. A flexible lead made of 2.54-μm Pt–10% Ir Teflon-coated wire connected the electrode with a percutaneous plug (Fig 1B). The percutaneous plug provided connection to an external current source. Control (n = 3) and stimulating (n = 3) electrodes of this design were implanted in the CN.

Operative Placement. Experiments were conducted in 18 pigmented guinea pigs, weighing 200 to 450 g,

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From the Department of Otolaryngology, Kresge Hearing Research Institute (Niparko, Altschuler, Wiler), and the Bioelectrical Sciences Laboratory, Department of Electrical Engineering (Xue, Anderson), University of Michigan, Ann Arbor. Supported by National Institutes of Health research contract N01 NS 5 2387. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Michigan, Ann Arbor.

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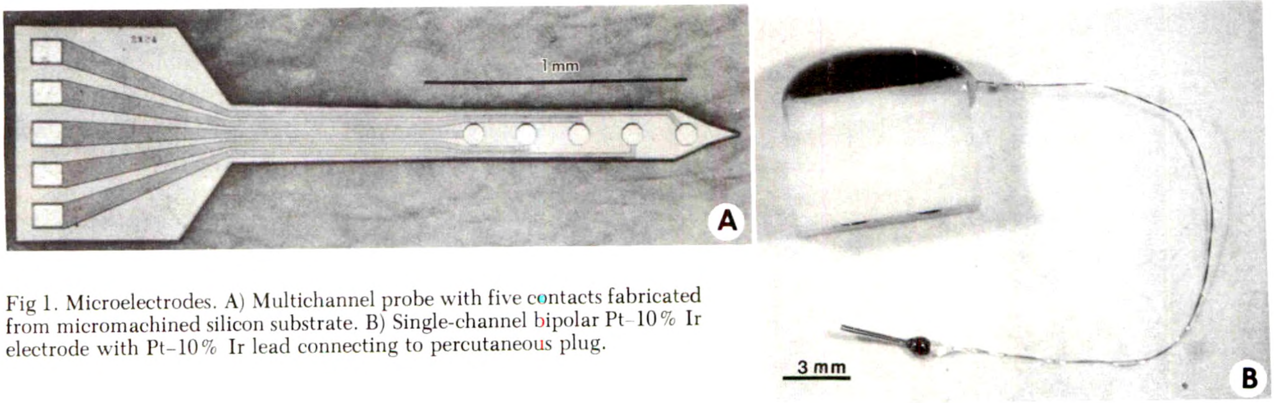

Fig 1. Microelectrodes. A) Multichannel probe with five contacts fabricated from micromachined silicon substrate. B) Single-channel bipolar Pt–10% Ir electrode with Pt–10% Ir lead connecting to percutaneous plug.

with active Preyer's reflex. Preoperative antibiotics (chloramphenicol, 1 mg/kg) and steroids (dexamethasone sodium phosphate, 0.1 mg/kg) were administered intramuscularly. This single dose of steroid was given to minimize brain stem edema from operative manipulation and electrode penetration. Guinea pigs were anesthetized with ketamine hydrochloride (20 mg/kg) and xylazine (0.2 mg/kg) intramuscularly for operative implantation.

The CN implantation was accomplished through a TB (n = 6) or SO (n = 12) approach. The TB approach entailed opening the dorsal bulla to expose the labyrinth. The vestibular labyrinth was drilled out to open the internal auditory canal and expose the cochleovestibular nerve. The cochleovestibular nerve was followed medially to its brain stem insertion, and the cochlear division was identified inferior to the vestibular division and caudal to the facial nerve. Microelectrodes were inserted 1 to 2 mm dorsomedial to the insertion of the cochlear division of the cochleovestibular nerve.

The SO approach entailed an occipitoparietal craniotomy lateral to the sagittal crest that exposed the floccular lobe and lateral cortex of the cerebellum. Medial retraction of the floccular lobe exposed the insertion of the cochleovestibular nerve. As with the TB approach, microelectrodes were inserted 1 to 2 mm dorsomedial to the cochlear nerve insertion.

To test the effects of tethering electrodes to the skull, a connecting Pt–10% Ir insulated wire was cemented to the skull surface with dental acrylic.

Electrophysiology. In three preparations, Pt–10% Ir single-channel electrodes were activated at the time of implantation. Prior to brain stem implantation, animals in this group received acoustic stimulation with broadband clicks at 107 dB sound pressure level at a rate of 100/s to establish the acoustically evoked response. Evoked potentials were recorded by use of an active recording screw electrode in the skull placed 1 cm lateral to the bregma on the side opposite the stimulated ear. Nape of neck and lower limb leads served as reference and ground electrodes, respectively. The resulting potential was amplified with a Grass P-15 preamplifier and a second-stage amplifier. The signal was averaged with a Modular Instruments Inc (MI^2) M202 Analog Input Module interfaced with an AT class computer.

During the electrode implantation procedure, far-field responses to direct stimulation were monitored similarly. A 150-μC/cm^2 real/phase charge-balanced biphasic pulse of 550 μs duration (200-μs activation pulse with a 350-μs charge-balancing pulse) was delivered at a rate of 20/s. Two hundred samples of 50 ms were used to obtain the average.

The baseline acoustic response and the electrical response with direct CN stimulation are shown in Fig 2. The acoustically derived response is comparable to the middle latency response (MLR). This response is of particular interest to us because, unlike the auditory brain stem response, its long latency of onset (10 to 50 ms) permits separation from the stimulus artifact.

Specimen Preparation. Three to 4 weeks after implantation the guinea pigs were heavily anesthetized with chloral hydrate and fixed via cardiac perfusion with phosphate buffer followed by 4% paraformaldehyde and 0.1% glutaraldehyde in phosphate buffer. Animals then were decapitated painlessly and the head was immersed in the fixative for approximately 24 hours. The cranium was opened

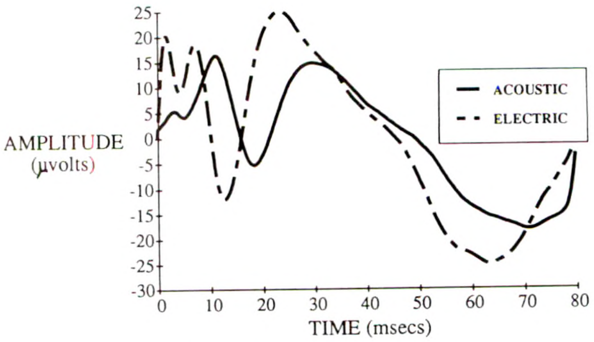

Fig 2. Comparison between acoustically and electrically evoked middle latency responses. Acoustic response was evoked by broadband clicks at 107 dB. Electrical response was evoked with stimulus intensity of 150 μA.

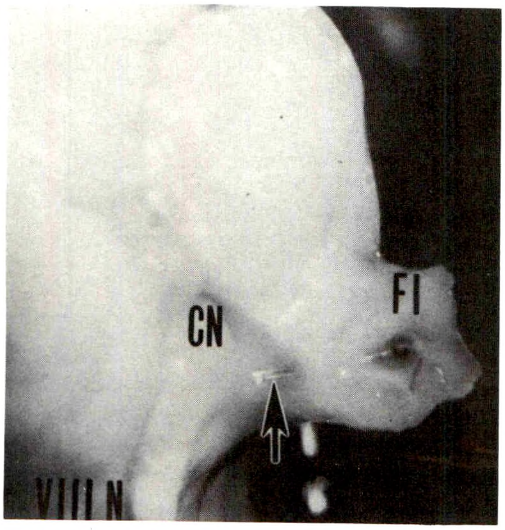

Fig 3. Postmortem specimen demonstrating Pt–10% Ir electrode embedded in floccular lobe of cerebellum (Fl) with electrode terminus lateral to cochlear nucleus (CN).

and the position of electrodes carefully noted in order to determine if gross migration had occurred. The brain stem was removed and when possible the electrode was left in place. The condition of the implant and the tissue surrounding the implant was assessed. The brain stem then was sectioned with a vibrating microtome (Vibratome). Sixty-micron serial sections were cut in a frontal plane, mounted on glass slides, and stained with cresyl violet. This stain was chosen in order to label and identify neurons. In one case, the electrode was not fully removed, but passed through the entire tissue-processing sequence and remained in one of the tissue sections. Sections then were examined under bright-field and differential interference contrast (Nomarski) optics.

A comparison of cell density between the implanted and nonimplanted CNs was performed by use of a morphometric work station consisting of an MTI Precision 81 camera and monitor on a Leitz Dialux photomicroscope mixed with an Altek Datatab high resolution monochrome graphics card and an AST AT class computer. The section of the CN containing the electrode track or the comparable division from the contralateral side was imaged on the monitor and its area calculated by tracing its outlines. The number of cells within the defined area then was counted with the focus adjusted to make sure all neurons containing nuclei were counted in the 60-μm section. Since the total area of the implanted side was less because of the space occupied by the electrode track, the comparison was made of density, not total number of neurons per section. Cell density measurements obtained with this method are computer-generated comparative figures. To determine if an effect was localized specifically to the area adjacent to the electrode track, density was determined also for an area whose lower boundary was demarcated by the superior margin of the electrode track (or a continuation thereof) and whose dorsal limit was a line parallel and 100 μm superior to the superior margin of the electrode track.

RESULTS

Tolerance of Implant Procedure. Results obtained in the initial phase of this project demonstrated poor tolerance of the TB approach to CN implantation. Three of six animals implanted through the TB approach died. All three animals demonstrated depressed activity levels postoperatively and died within 48 hours of operation. Twelve animals were implanted by the SO approach to the CN. Only one mortality resulted from this procedure.

In most cases, surviving animals implanted through either the TB or SO approach demonstrated gait ataxia and dysmetria of the head when attempting to feed for 24 to 48 hours following operation. These adverse findings subsequently disappeared. Both the TB and SO approaches afforded adequate exposure of the CN target.

Response to Electrical Stimulation. Stimulation of the implanted electrode was performed in three animals receiving the single-channel Pt–10% Ir implant. During stimulus trials no adventitious motor responses were elicited. Facial and limb movement, mandibular excursion, nystagmus, and changes in respiratory patterns were absent during periods of stimulation.

Far-field recordings demonstrated no response to stimulation when the electrode terminus was placed on adjacent bone or cerebellum. Following placement of the electrode into the CN under microscopic visualization, recordings demonstrated multiple peaked waveforms. Monitored responses varied in morphology with depth of electrode penetration. A comparison of electrically evoked MLR with CN stimulation and auditory evoked MLRs is seen in Fig 2. Electrically derived responses demonstrated shorter latencies than did acoustic responses.

POSTMORTEM ANALYSIS AND HISTOLOGIC RESPONSE

Electrode Placement. Evidence suggesting electrode migration was noted in three animals implanted with microelectrodes (one untethered and two tethered preparations). The migration appeared to be in a lateral direction (Fig 3) in these animals.

Histologic assessment revealed tissue tracks through the CN with both multichannel Si substrate and single-channel Pt–10% Ir microelectrodes. Tracks were seen in all divisions of the CN, predominantly in the ventral CN. In the majority of preparations the electrode tracks were confined to the CN, although in two cases, the tracks demon-

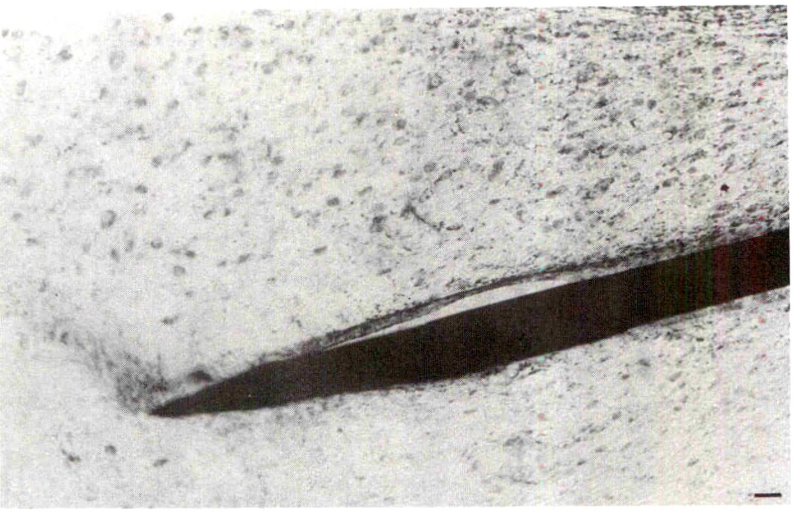

Fig 4. Sixty-micron section through cochlear nucleus containing silicon substrate electrode. Note minimal tissue reaction. Bar — 50 µm.

strated deep penetration with passage into the inferior cerebellar peduncle or vestibular tract. Consistently, placement in the CN was achieved in the group of three animals in which intraoperative monitoring was available. Overall, 11 of 14 surviving animals showed electrode tracks in the CN.

Tissue Reaction. In five animals with successful placement of the untethered Si substrate electrode in the CN, a thin rim of fibrous tissue with some glial proliferation, never exceeding 15 µm, was seen along the electrode track. No glial proliferation beyond the immediate area of the electrode track was evident. Inflammatory cell migration adjacent to the electrode track was absent in all preparations regardless of electrode material. Histologic evaluation demonstrated no signs suggestive of neuronal damage such as shrinkage, increased staining density, or vacuolization (Fig 4). The results in three animals with tethered Si substrate electrodes were similar. In three guinea pigs with successful CN placement of tethered Pt–10% Ir electrodes there was a thin rim of fibrous tissue along the electrode track, never exceeding 15 µm in width (Figs 4 and 5). The tissue adjacent to the electrode track demonstrated excellent cell preservation and no reactive cellular infiltration. Tissue reaction therefore varied little with the type of electrode implanted or with electrode tethering to the skull and was judged to be minimal.

The density of cells in implanted CNs in both whole sections and the region adjacent to the electrode track was within a 10% variation of the cell density in the unimplanted side. Neuronal density in preparations implanted with tethered electrodes was similarly consistent with that seen in unimplanted CNs (variation $\leq 10\%$). There was therefore considered to be no substantial loss of neurons in the CN adjacent to the electrode, except perhaps for those in the actual site of the electrode track.

DISCUSSION

The major synaptic centers within the ascending central auditory pathway are the CN, superior olivary complex, inferior colliculus, medial geniculate body, and auditory cortex. Neuroprosthetic stimulation of several of these areas has been studied with varied approaches. Previous studies have examined the feasibility and usefulness of stimulation of the auditory cortex,[5,6] inferior colliculus,[7] and CN surface[1-4] to effect audition.

The primary auditory cortex is located on the transverse temporal gyrus (gyrus of Heschl) on the dorsal surface of the superior temporal convolution. Surgical exposure of this area is hampered by its location deep within the floor of the lateral sulcus adjacent to the middle cerebral artery. The relatively large surface area of the auditory cortex also limits the usefulness of this site for implantation. Intraoperative stimulation of cortical sites has demonstrated that perceived sounds are monotonous and devoid of dynamic qualities.[5,6]

The inferior colliculus lies on the dorsal surface of the midbrain. Intraoperative stimulation of the inferior colliculus was performed by Simmons et al[7] in a patient undergoing resection of a recurrent cerebellar tumor. Direct stimulation of the inferior colliculus produced no auditory percept.

The CN is located in the ventrolateral aspect of the caudal pons and receives input from cochlear nerve afferent fibers. The CN surface lies adjacent to the lateral recess of the fourth ventricle and is flanked by the cerebellum, pons, and medulla. Within the pontine brain stem, vestibular and pontobulbar nuclei and the middle and inferior cerebellar peduncles lie adjacent to the CN. Dorsal and ventral divisions of the CN are apparent on gross and microscopic inspection. Cells with nuclei in the CN receive terminals of the primary auditory afferent fibers. The CN contains large numbers of projection neurons that give rise to the ascending auditory pathways. There is a wide frequency representation in the ventral CN, with several complete tonotopic representations.[8,9] Fibers with high and

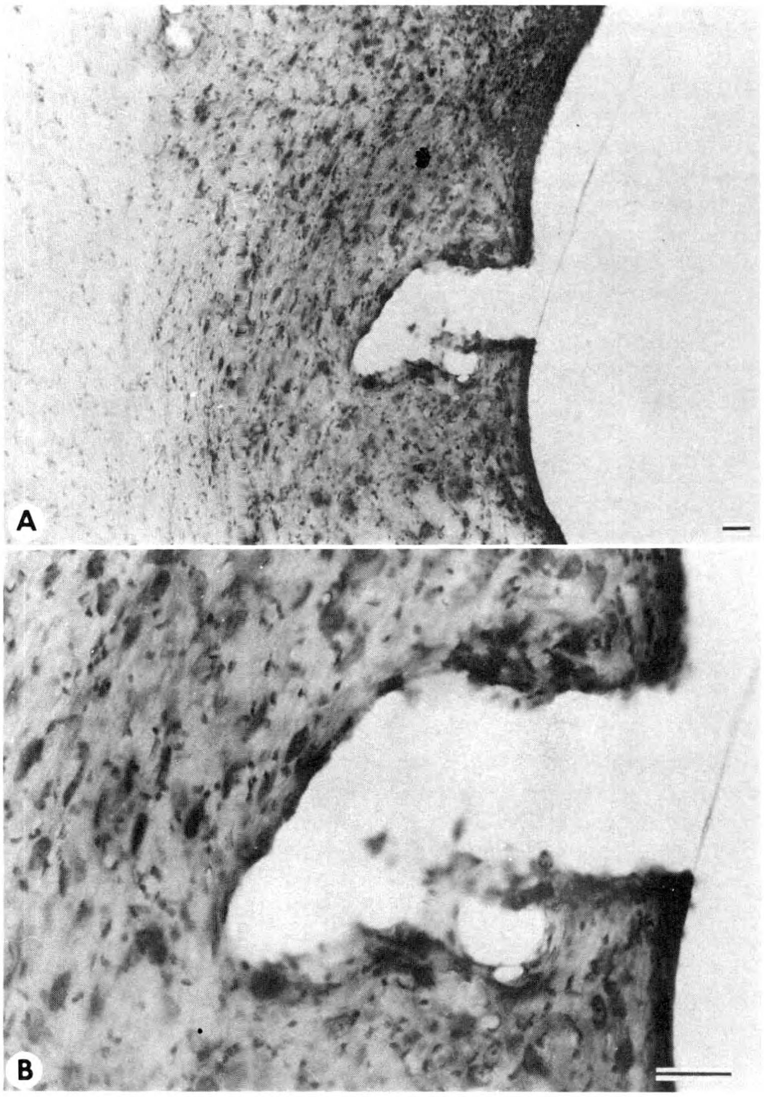

Fig 5. Sixty-micron section through cochlear nucleus of guinea pig with Pt–10% Ir electrode implant. Bars — 50 μm. A) Electrode track showing minimal tissue reaction. B) Higher magnification of A.

low frequency representations are distributed in the posterodorsal and anteroventral aspects, respectively, in different divisions of the ventral CN.[8-10] Thus, it would appear that the ventral CN would be an ideal site for implantation to stimulate higher auditory centers in the absence of peripheral auditory structures.

Ongoing investigations at the House Ear Institute have provided evidence that the CN may be a useful site for auditory prosthesis implantation.[1-4] Experience with von Recklinghausen's patients implanted with CN surface electrodes has demonstrated that limited differential intensity and pitch discrimination is achievable with this prosthesis.[2,3] Speech pattern contrast testing of these patients has demonstrated above-chance scores on suprasegmental and consonant voicing subtests.[3] Although minimal speech discrimination is produced, environmental contact and improved speech reading have been achieved.

The present study was undertaken to examine the feasibility of implanting the CN with a penetrating prosthesis. Similar to use of multichannel scala tympani electrodes, this approach may provide access to tonotopically arranged neural pathways. In addition to possibly enhancing pitch perception, close contact with cell bodies would also reduce the current flow necessary to achieve activation. This would decrease the power requirements and decrease the likelihood of activating adjacent neural pathways.

Our results suggest that the CN implantation procedure in this animal model is substantially better tolerated through a posterior (SO) approach. The lateral (TB) approach may introduce a large CSF leak following removal of the lateral confines of the cerebellopontine space. The presence of a foreign body, in this case the prosthetic device, may have prevented spontaneous closure of the bullar defect. No attempt was made to close the bullar defect with soft tissue. Therefore, these findings should be extrapolated with caution when considering CN implantation in higher animal models and humans.

Histologic results suggest that electrode placement within the CN is feasible via external approaches, although the accuracy of placement within the ventral CN was somewhat variable. The use of intraoperative monitoring enhanced the accuracy of placement within the CN. We have noted, however, that the level of anesthesia can markedly affect the appearance of evoked responses obtained with such monitoring. Reliable use of this modality for monitoring implantation will require clarification of the effects of anesthetics on potentials evoked by direct stimulation of the CN.

No difference in the pattern of the tissue response to tethered versus untethered electrodes was seen. These findings suggest that little, if any, probe motion was induced by forces applied by the lead wire.

Previous studies have demonstrated tissue tolerance of Pt-Ir microelectrodes placed in cortical sites with and without stimulation.[11,12] The present histopathologic findings demonstrate excellent tissue tolerance of Si substrate microelectrodes as well as Pt–10% Ir penetrating electrodes in the CN. The pattern of tissue response did not vary with electrode materials or with transient intraoperative stimulation.

These pilot experiments have demonstrated the potential for microelectrode migration. In contrast to cerebral and cerebellar cortex electrodes, the CN electrode is placed in a fluid-filled recess — the cerebellopontine angle — that lacks an immediate bony or fibrous tissue covering for stabilizing the implant. Our observations of the operative procedure and postmortem results suggest that some combination of the following factors may contribute to electrode migration.

1. Operative exposure of the brain stem induces a variable amount of tissue edema that, with resolution, may shift the relative position of the implant.
2. Brain pulsation, the natural tendency of the brain to move within the CSF compartment with vascular pulsations, likewise may shift the relative position of the implant.
3. The contraction of dura and other soft tissue overlying the craniotomy may produce traction forces on the implant or the attached conductors.

In our series, electrode migration occurred with both tethered and untethered implants. This suggests that the tether cannot be depended upon to maintain electrode position. It appears that positional stability can be achieved only at the electrode-tissue interface. We therefore are evaluating alternative methods of electrode fixation as well as new electrode designs to minimize migration. Alternate biomaterials such as pure gold that can be used to manufacture an ultraflexible tether[12] are under consideration.

Selecting the optimal anatomic approach and technique of surgically implanting the CN will require consideration of multiple factors. The ideal operative method will allow accurate electrode placement and adequate stabilization for the implanted electrode and attached wire and will provide the capacity to monitor the selectivity and efficacy of auditory tract stimulation intraoperatively. While not definitive, intraoperative MLR monitoring does, in conjunction with other observations, help to confirm proper placement. Generally, electrically evoked MLR waveforms conform to acoustically evoked MLRs, with the exception of artifact and latency.

The results of the present study support the feasibility of implanting a neuroprosthesis in the CN and have helped to establish implant strategies for further studies of chronic stimulation.

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REFERENCES

1. Hitselberger WE, House WF, Edgerton BJ, Whitaker S. Cochlear nucleus implant. Arch Otolaryngol 1984;92:52-5.

2. Edgerton BJ, House WF, Hitselberger W. Hearing by cochlear nucleus stimulation in humans. Ann Otol Rhinol Laryngol 1982;91(suppl 91):117-24.

3. Eisenberg LS, Maltan AA, Portillo F, Mobley JP, House WF. Electrical stimulation of the auditory brainstem structure in deafened adults. J Rehabil Res Dev 1981;24:9-22.

4. McElveen JT, Hitselberger WE, House WF, Mobley JP, Terr LI. Electrical stimulation of cochlear nucleus in man. Am J Otol 1985;6(suppl 1):88-91.

5. Penfield WT, Rasmussen TR. The cerebral cortex of man. New York: Macmillan, 1950.

6. Dobelle WH, Stensaas SS, Mladejovsky MG, Smith JB. A prosthesis for the deaf based on cortical stimulation. Ann Otol Rhinol Laryngol 1973;82:445-63.

7. Simmons FB, Mongeon CJ, Lewis WR, Huntington D. Electrical stimulation of the acoustical nerve and inferior colliculus. Arch Otolaryngol 1964;79:559-67.

8. Moore JK. Cochlear nuclei: relationship to the auditory nerve. In: Altschuler RA, Bobbin RP, Hoffmann DW, eds. Neurobiology of hearing. The cochlea. New York: Raven Press, 1986: 283-301.

9. Moore JK, Osen KK. The cochlear nuclei in man. Am J Anat 1979;154:393-417.

10. Dublin WB. Central auditory pathology. Otolaryngol Head Neck Surg 1986;95:363-424.

11. Agnew WF, Yuen TGH, McCreery DB, Bulbara LA. Histopathologic evaluation of prolonged intracortical electrical stimulation. Exp Neurol 1986;92:162-85.

12. Salcman M, Bak MJ. A new chronic recording intracortical microelectrode. Med Biol Eng 1976;14:42-50.

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OSTEOSARCOMA OF THE LARYNX

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A case of laryngeal osteosarcoma in a 75-year-old man is described. The osteosarcoma probably arose by dedifferentiation of a chondrosarcoma of the cricoid cartilage. Laryngeal osteosarcoma is rare: the literature is reviewed and management discussed.

KEY WORDS — chondrosarcoma, larynx, osteosarcoma.

INTRODUCTION

Osteosarcoma is the rarest of the laryngeal sarcomas[1]; only eight cases have been described.[2-9] In several of these the pathologic details are poorly documented. We report a case of osteosarcoma, probably arising by dedifferentiation of a low-grade chondrosarcoma of the cricoid cartilage, with detailed recording of the pathologic findings.

CASE REPORT

A 75-year-old man presented in April 1985 with discomfort in his throat and minor dysphagia. There was no stridor at that time. Indirect laryngoscopy revealed a large mass, covered by normal mucosa, filling the left pyriform fossa. The left vocal cord was fixed, and there was a small polyp on the outer half of the left vocal cord. No nodes

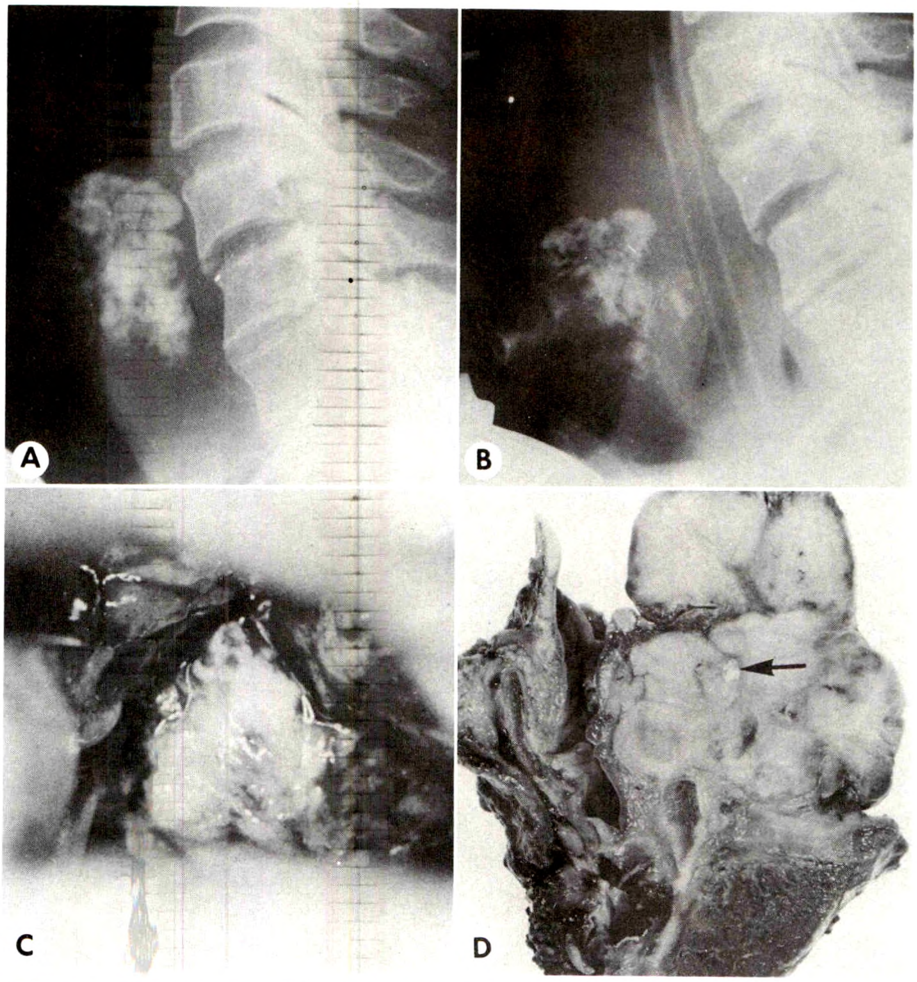

Fig 1. A,B) Lateral soft tissue radiographs of neck. A) In January 1987, showing calcified mass between spine and cricoid cartilage. B) In November 1987, showing decreased calcification compared with A. C) Photograph by indirect laryngoscopy, showing airway obstruction by left-sided mass. D) Sagittal section of tumor, showing airway narrowing with intact mucosa. Pale foci of chondroid tissue are present (arrow).

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pears to have arisen in the cricoid cartilage.[4] Chondrosarcomas of the larynx are less rare,[3] but are usually of low-grade malignancy and grow slowly. Dedifferentiation to high-grade osteosarcoma has not been described in detail before in the larynx, although a case of dedifferentiated laryngeal chondrosarcoma is mentioned briefly by Dahlin and Unni.[13]

Osteosarcomas are typically highly malignant neoplasms that metastasize early. Our case had already metastasized to the epiglottis, and venous invasion was seen. Therefore we believe that chemotherapy might improve the prognosis for this patient: the cure rate for patients with nonmetastatic osteosarcoma of bone treated by ablative surgery and/or radiotherapy is only 20%.[13,14] However, the addition of chemotherapy has raised the disease-free survival to between 45% and 90%[15-19] after 5 years.

REFERENCES

1. Kleinsasser O. Pathology of the larynx. Stuttgart, Federal Republic of Germany: Springer-Verlag, 1984:358-61.

2. Clerf LH. Sarcoma of the larynx — report of eight cases. Arch Otolaryngol 1946;44:517-24.

3. Gorestein A, Neel HB, Weiland LH, Devine KD. Sarcomas of the larynx. Arch Otolaryngol 1980;106:8-12.

4. Haar JG, Chaudhry P, Karanjia MD, Milley PS. Chondroblastic osteosarcoma of the larynx. Arch Otolaryngol 1978;104:477-81.

5. Morley AR, Cameron DS, Watson AJ. Osteosarcoma of the larynx. J Laryngol Otol 1973;87:997-1005.

6. Remagen W, Lohr WJ, von Westernhagen B. Osteosarkom des Kehlkopfes. HNO 1983;31:366-8.

7. Sprinkle PM, Allen MS, Brookshire PF. Osteosarcoma of the larynx. (A true primary sarcoma of the larynx.) Laryngoscope 1966;76:325-33.

8. Succhatlampong V, Striumpai S, Khawcharoenporn V. Osteosarcoma of the larynx. The first case report in Thailand with ultrastructural study. J Med Assoc Thai 1981;64:301-7.

9. Dahm LJ, Schaefer SD, Larder HM, Vellios F. Osteosarcoma of the soft tissues of the larynx. Cancer 1978;42:2343-51.

10. Chung EB, Enzinger FM. Extraskeletal osteosarcoma. Cancer 1987;60:1132-42.

11. Dahlin DC, Coventry MB. Osteogenic sarcoma. A study of 600 cases. J Bone Joint Surg [Am] 1967;49:101-10.

12. McCarthy EF, Dorfman HD. Chondrosarcoma of bone with dedifferentiation: a study of eighteen cases. Hum Pathol 1982;13:36-40.

13. Dahlin DC, Unni KK. Bone tumors. 4th ed. Springfield, Ill: Charles C Thomas, Publisher, 1986:245.

14. Friedman MA, Carter SK. The theory of osteogenic sarcoma: current status and thoughts of the future. J Surg Oncol 1972;4:482-510.

15. Cortes EP, Holland JF, Glidewell O. Amputation and Adriamycin in primary osteosarcoma: a 5-year report. Cancer Treat Rep 1978;62:271-7.

16. Jaffe N, Frei E III, Watts H, Traggis D. High-dose methotrexate in osteogenic sarcoma: a 5-year experience. Cancer Treat Rep 1978;62:259-64.

17. Rosen G, Caparros B, Huvos AG, et al. Preoperative chemotherapy for osteogenic sarcoma: selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy. Cancer 1982;49:1221-30.

18. Winkler K, Beron G, Kotz R, et al. Neoadjuvant chemotherapy for osteogenic sarcoma: results of a cooperative German/Austrian study. J Clin Oncol 1984;2:617-24.

19. Link M, Goorin A, Miser A, et al. The role of adjuvant chemotherapy in the treatment of osteosarcoma (OS) of the extremity: preliminary results of the multi-institutional osteosarcoma study (MIOS). Proc Am Soc Clin Oncol 1985;4:237.

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THIRD INTERNATIONAL SYMPOSIUM AND WORKSHOPS ON SURGERY OF THE INNER EAR

The Third International Symposium and Workshops on Surgery of the Inner Ear will be held July 29-August 4, 1990, in Snowmass-Aspen, Colorado. For further information, contact Maurine Taylor, c/o I. Kaufman Arenberg, MD, 300 East Hampden Avenue, Suite 401, Englewood, CO 80110.

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IMMUNE RESPONSE OF THE ENDOLYMPHATIC SAC TO HORSERADISH PEROXIDASE: IMMUNOLOGIC ROUTE FROM THE MIDDLE EAR TO THE INNER EAR

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Twenty guinea pigs were immunized with horseradish peroxidase (HRP) intradermally and challenged with 5 mg of the same antigen in the tympanic bulla. The appearance of immunoglobulin-producing cells (plasma cells) in the inner ear structure was examined immunohistochemically in frozen sections. Four to 10 days following antigen challenge, 5 of the 20 animals showed significantly increased plasma cells in the subepithelial connective tissue of the endolymphatic sac (ES). Those cells showed positive reactions, mainly with IgG followed by IgM. The cells that reacted positively with IgA were few. Some of these plasma cells were considered to contain the specific antibody against HRP. The results indicate the role of the ES as a local immune response region for the inner ear complex, as well as the existence of an immunologic route from the middle ear cavity to the inner ear, particularly to the ES.

KEY WORDS — endolymphatic sac, immune response, immunohistochemistry, inner ear.

INTRODUCTION

Recently, several authors have indicated that the inner ear is immunocompetent. Mogi et al[1] identified a significant increase of antibody titers in perilymph of animals sensitized with egg albumin. This experiment indicated that the increased antibody in perilymph was derived systemically from perilymphatic blood vessels as a filtrate. The subsequent experiments of Harris[2] revealed an increase of specific antibody in perilymph against antigen in the challenged cochlea, and it was regarded to be independent of the cerebrospinal fluid and the influence of increased vascular permeability. He postulated the existence of a local immune response system in the inner ear.

Tomiyama and Harris[3] and Morgenstern et al[4] studied the immune function of the endolymphatic sac (ES) by using guinea pigs that had undergone unilateral obliteration of the ES and had been systemically sensitized to keyhole limpet hemocyanin (KLH). Following local or systemic antigen challenge, the anti-KLH antibody titers in the endolymph and/or perilymph were measured, and the reduction of antibody titers in the inner ear fluids obtained from the ears with obliterated ESs was shown. Results indicated the possibility that the ES was an immunocompetent organ of the inner ear.

Morphologic investigations of the ES at the ultrastructural level by Rask-Andersen and Stahle[5] and D. J. Lim and P. Silver (unpublished observations) showed that the richly vascularized connective tissue of the ES contained monocytes, lymphocytes, and occasional plasma cells; and the existence of an immunologic interaction of macrophages and lymphocytes was suspected by the investigators.[5] Moreover, recent immunohistochemical studies on the normal ES of humans[6] or of guinea pigs[4,7] have shown that the ES richly contains immunoglobulin.

Saijo and Kimura[8] have reported that HRP applied to the middle ear cavity of the guinea pig passed through the round window membrane into the perilymphatic space and afterward was found in the ES as well as in the endolymphatic space of the inner ear. The Reissner's and saccular membranes were believed to be the routes from perilymph to endolymph, and the vestibular aqueduct was believed to be the route to the ES. Lim[9] also introduced horseradish peroxidase (HRP) into the tympanic bulla of the chinchilla and found HRP phagocytosed in macrophages in the ES. He proposed that the HRP must be transported to the ES through the perisaccular space of the endolymphatic duct. Lim emphasized, moreover, that this finding profoundly implicated the ES in the immune mechanism of the inner ear.

The main purpose of this study was to explore the reason for the local immune response of the inner ear by means of immunohistochemical methods. The antigen of this study, HRP, was introduced into the middle ear cavity to allow possible spontaneous penetration through the round window membrane into the inner ear. To avoid nonspecific reactions, the antigen was not produced by direct mechanical damage to the inner ear structures. The technique used also makes it possible to observe an immunologic route from the middle ear cavity to the inner ear.

MATERIALS AND METHODS

IMMUNIZATION

Horseradish peroxidase (type VI, Sigma Chemical) was employed as the antigen. Twenty female

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colored guinea pigs weighing between 200 and 250 g with normal Preyer's reflex were employed and immunized intradermally with 1 mg HRP in 0.05 mL physiologic saline solution with 0.05 mL complete Freund's adjuvant twice, once a week. After 4 weeks, the tympanic bullae of these animals were exposed by a retroauricular approach under intraperitoneal pentobarbital anesthesia (45 mg/kg). One middle ear cavity was challenged with 5 mg HRP in 0.1 mL physiologic saline, and the other was provided with 0.1 mL physiologic saline as a negative control.

TISSUE PREPARATIONS

On day 2 following antigen challenge to the middle ear cavity, we examined three animals; on days 4, 7, and 10 we examined five animals each day; and on day 21 we examined two animals. The animals were heart-punctured for their serum sampling and killed with intracardiac perfusion with 4% paraformaldehyde in 0.85% NaCl with 2% acetic acid.[10,11] The temporal bones were removed immediately and immersed in the same solution for 6 days. Decalcification of the bone was performed through this process by acetic acid. After being rinsed in phosphate-buffered saline (PBS), the temporal bones were embedded in a medium for frozen tissue specimens (Tissue-Tec II, Miles Laboratory), frozen and sectioned in a cryostat to 6 to 8 μm thickness, and mounted on a glass slide previously coated with 0.01% poly-L-lysine (Sigma Chemical).

IMMUNOLOGIC STUDIES

Measurement of Antibody Titer of Sera With ELISA. Twenty serum samples from immunized guinea pigs and four from normal guinea pigs were diluted 1:100 in PBS. The microtiter wells (Greiner Labor-Technik) were incubated with 0.01% HRP for 12 hours at 4°C and reacted with the diluted sera for 2 hours, with protein-A conjugated with alkaline phosphatase (1:400) (Bio-Yeda) for 1 hour, and with *p*-nitrophenyl phosphate for 1 hour. The optical density of the microtiter wells was read at 405 nm of optical interference filter on a spectrophotometer (Cambridge Technology, Inc).

Immunohistochemical Studies. The cells containing immunoglobulins (IgG, IgM, and IgA) were detected by the avidin-biotin complex (ABC) technique.[12] Glucose oxidase (GO) was chosen as the enzyme marker[13] (Vector Laboratories). As the primary antibodies, goat anti guinea pig IgG (Fc) (1:1,000), sheep anti guinea pig IgM (Fc) (1:300), and sheep anti guinea pig IgA (Fc) (1:300) (Nordic Immunology) were used, and as the secondary antibodies, biotinylated rabbit anti goat IgG (1:20) and rabbit anti sheep IgG (1:20) (Vector Laboratories) were used. The sectioned tissue previously incubated with normal rabbit serum (1:2) for 30 minutes was reacted with the primary antibody for 90 minutes, with the secondary antibody for 1 hour, and with ABC-GO for 45 minutes. Then the tissue was reacted with nitroblue tetrazolium (NBT, Vector Laboratories) for 25 minutes, and the positive reaction was exhibited in blue. After counterstaining with nuclear-fast red, slides were dehydrated in graded alcohol, cleaned in xylol, embedded in Eukitt, and examined under a light microscope.

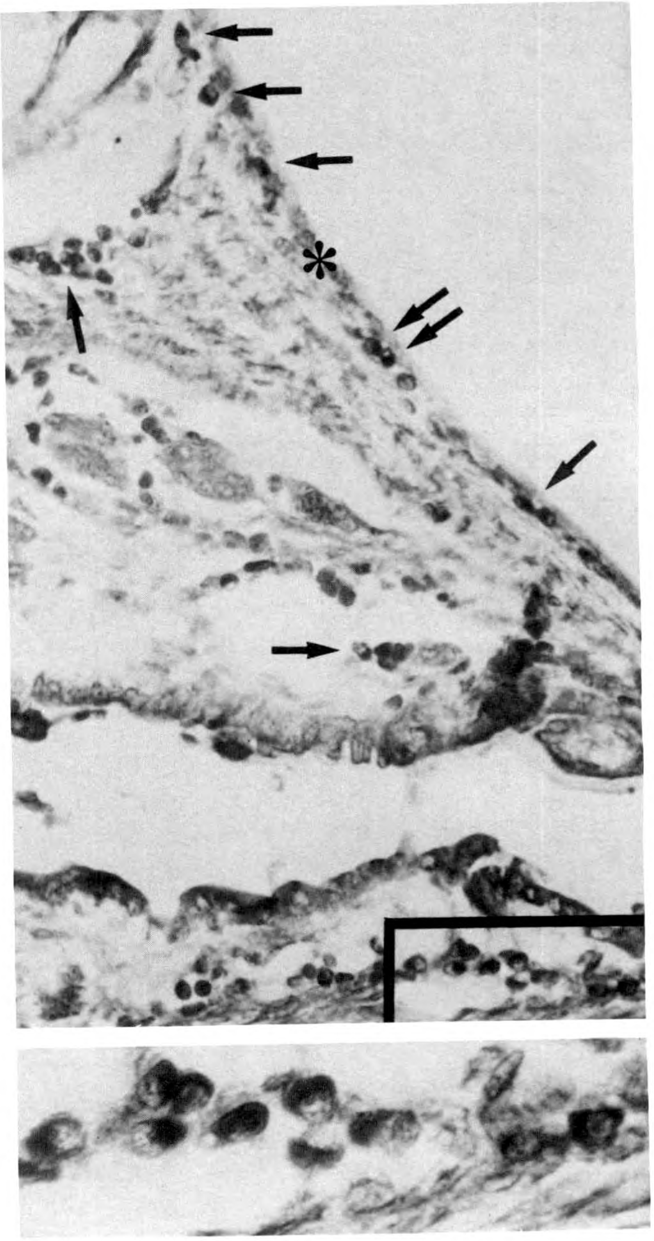

Fig 1. Photomicrographs of plasma cells located along lateral wall of sigmoid sinus (asterisk) as well as in perisaccular connective tissue and exhibiting positive cytoplasmic reaction with anti-immunoglobulin G antiserum: some cells are indicated by arrows (original x200). Positive plasma cells in cluster in rectangular area are magnified in micrograph below (original x500).

As a positive control, small intestine was used. As negative controls, PBS and normal sera from the same species of animals from which the primary an-

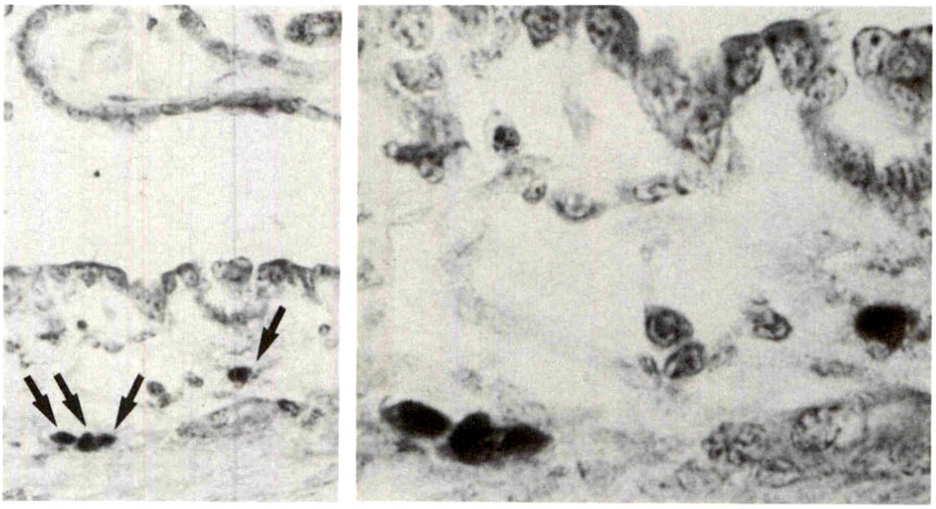

Fig 2. Photomicrographs of plasma cells in perisaccular connective tissue exhibiting positive cytoplasmic reaction with anti–immunoglobulin M antiserum (arrows) (original x200). Positive plasma cells on left micrograph are magnified on right (original x500).

tibodies were produced were used instead of primary antibodies.

The antigen for the detection of anti-HRP antibody synthesizing cells[14] was biotinylated peroxidase (Sigma Chemical). The sectioned tissue previously incubated with normal rabbit serum (1:2) for 1 hour was exposed to 0.1% biotinylated peroxidase overnight at 4°C and reacted with ABC-GO for 1 hour and with NBT for 30 minutes and counterstained with nuclear-fast red.

RESULTS

SERUM ANTI-HRP ANTIBODY TITER

The mean value of the titer (optical density) of immunized guinea pigs was 0.148 ± 0.068 (mean ± SD). The mean value was higher than that of normal guinea pigs (0.043 ± 0.005) with a statistically significant difference ($p < .01$).

IMMUNOHISTOCHEMICAL STUDIES

In four guinea pigs, killed on days 7 to 10 after antigen challenge, an increased number of plasma cells was observed in the subepithelial connective tissue of the ES, but no plasma cells were recognized in the lumen of the ES. One animal that was killed on the fourth day showed similar findings in the ES, with a relatively small number of plasma cells in the connective tissue. The location of the cells was always in the extraosseous part of the ES, regardless of the rugose or smooth portion. Those plasma cells reacted mostly with IgG (Fig 1), followed by IgM (Fig 2). The cells that reacted positively with IgA were few (Fig 3). These findings were significant compared with the normal findings observed in the opposite control ears, which showed no or very few plasma cells in the connective tissue of the ES. In both the boosted and control ears, some of the epithelial cells and some of the intraluminal cells of the ES, which were mostly macrophages, showed positive reactions with IgG, with IgM, and slightly with IgA. As additional findings, increased plasma cells were found simultaneously along the lateral wall of the sigmoid sinus adjacent to the ES in two guinea pigs (Fig 1). In one animal killed on day 7, very few plasma cells were recognized in the modiolus of the cochlea; however, no plasma cells were observed in the vestibule or in the

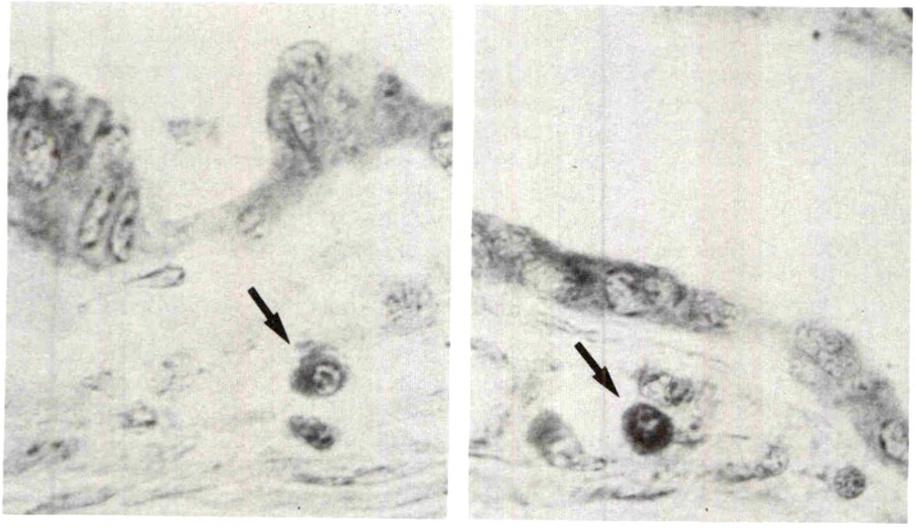

Fig 3. Two plasma cells (arrows) observed in perisaccular connective tissue in rugose (left) and smooth (right) portions and reacting positively with anti–immunoglobulin A antiserum (original x500).

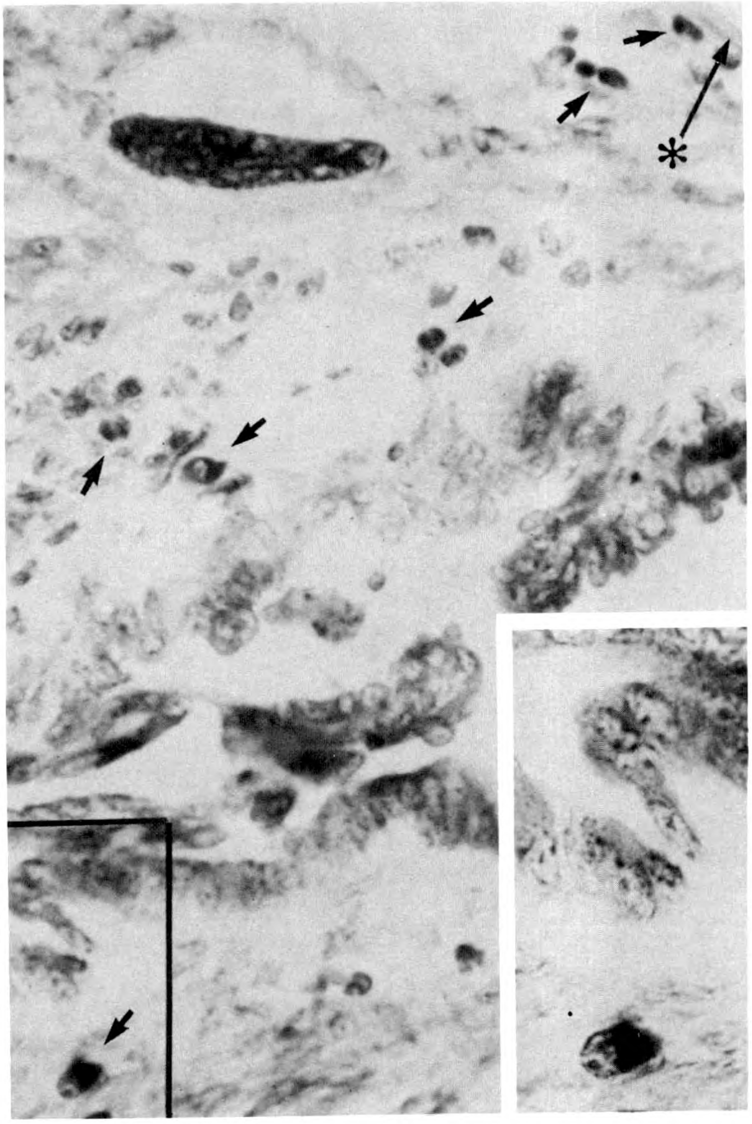

Fig 4. Plasma cells reacting with biotin-conjugated peroxidase (arrows) (original x300). These cells are located near lateral wall of sigmoid sinus (asterisk), as well as in subepithelial connective tissue of endolymphatic sac. Inset) High magnification of plasma cell in rectangular area, exhibiting strongly positive cytoplasmic reaction (original x500).

ampullated ends of the semicircular canals in any of the 20 animals.

Some of the plasma cells in the perisaccular connective tissue and the wall of the sigmoid sinus showed positive cytoplasmic reactions with biotinylated peroxidase, to which they were exposed on the sectioned tissue (Fig 4). This finding was not observed in the control ears.

DISCUSSION

In the present study, guinea pigs that previously had been sensitized to HRP and showed a significant increase of anti-HRP antibody titer in the sera showed a sufficient number of plasma cells in the subepithelial connective tissue of the ES following the challenge of the same antigen into the middle ear cavity. Moreover, it was demonstrated that some of these plasma cells reacted positively with biotin-conjugated peroxidase on the frozen sections. Hence these cells were assumed to be synthesizing specific anti-HRP antibody on the sites. These results confirmed the role of the ES as a local immune response organ for the inner ear complex, and also directly indicated the occurrence of immunologic intercourse from the middle ear to the inner ear, particularly to the ES.

We do not assume that those plasma cells were derived from other parts of the inner ear or from the middle ear and reached the ES with a possible longitudinal flow of endolymph or by diffusion, since we did not find plasma cells either in the lumen of the ES or in the endolymphatic or perilymphatic space of the inner ear. We conclude that the plasma cells originated in the perisaccular region of the ES, which has been proved to be rich not only in blood vessels and lymph vessels, but also in lymphocytes.[5]

Through this study, we did not find clearly positive responses of immune-producing cells in the cochlea or in the vestibule. In addition to the peculiar ultrastructural findings of the perisaccular connective tissue,[5] the response of the ES may result from its characteristic anatomic location. The ES is on the terminal end of the endolymphatic system of the inner ear complex, which is widely accepted to possibly have a longitudinal flow of endolymph. We assume that the ES, as a terminal structure, can collect a greater amount of antigenic substances that remain there for a longer period of time than can other parts of the inner ear. The amount of the antigen and its prolonged local duration are very important factors for stimulating the local immune response. This is well known as one of the reasons the antigen usually is provided locally with some adjuvant for immunization.

According to Harris and Ryan,[15] specific antibody response was observed in the perilymphatic space of previously sensitized guinea pigs following the antigen challenge to the middle ear cavity. The authors indicated this may have been due to the passage of the antigen from the middle ear to the inner ear. According to the results of our experiment, we support their assumption and suggest that some of the increased antibody in perilymph of their experiment was derived from the inner ear complex and that presumably the ES played an important role.

In some animals we found increased plasma cells along the lateral wall of the sigmoid sinus facing the ES of the challenged ear. This finding suggests an immunologic relationship between the sigmoid sinus and the ES. This point requires further study.

The results of the present study demonstrate the existence of an immunologic route from the middle ear to the inner ear, particularly to the ES, in which local immune response can occur. Therefore we assume that in some cases, for instance chronic inflammation of the middle ear, if there are such antigenic substances as can pass through the round window membrane, they may reach the ES and repeatedly introduce immunologic reactions to the ES. It is known that inappropriate activation of immune mechanisms can result occasionally in hypersensitivity and tissue damage rather than immunity. As a result, under some conditions, immune reactions in the ES might introduce pathologic changes in the ES itself. The damaged ES, as a matter of course, could be assumed to have a disorder of its normal functions, eg, endolymph absorption or pressure regulation of the inner ear. This assumption might be very suggestive when we consider endolymphatic hydrops, which is observed simultaneously in some patients with chronic otitis media, as reported by Paparella et al.[16] Furthermore, the local immune response of the ES could help to explain to some extent why immune endolymphatic hydrops occurs in some clinical[17] and experimental[18,19] investigations.

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REFERENCES

1. Mogi G, Lim DJ, Watanabe N. Immunologic study on the inner ear. Immunglobulins in perilymph. Arch Otolaryngol 1982; 108:270-5.

2. Harris JP. Immunology of the inner ear: evidence of local antibody production. Ann Otol Rhinol Laryngol 1984;93:157-62.

3. Tomiyama S, Harris JP. The role of the endolymphatic sac in inner ear immunity. Acta Otolaryngol (Stockh) 1987;103: 182-8.

4. Morgenstern C, Ikeda M, Ninoyu O, Koldovsky P. The role of the endolymphatic sac in immune response of the inner ear. In: Veldman JE, ed. Immunobiology, histophysiology, tumor immunology in otorhinolaryngology. Amsterdam: Kugler Publications, 1987:131-9.

5. Rask-Andersen H, Stahle J. Immunodefence of the inner ear? Lymphocyte-macrophage interaction in the endolymphatic sac. Acta Otolaryngol (Stockh) 1980;89:283-94.

6. Arnold W, Pfaltz R, Altermatt H. Evidence of serum antibodies against inner ear tissue in the blood of patients with certain sensorineural hearing disorders. Acta Otolaryngol (Stockh) 1985;99:437-44.

7. Yamane H, Nakai Y, Sugiyama M, Konishi K, Takahashi K. The occurrence of IgG in the endolymphatic sac of the guinea pig. Arch Otorhinolaryngol 1987;243:370-3.

8. Saijo S, Kimura RS. Distribution of HRP in the inner ear after injection into the middle ear cavity. Acta Otolaryngol (Stockh) 1984;97:593-610.

9. Lim DJ. Functional morphology of the tympanic membrane and tubotympanum. With emphasis on immunobiology. In: Veldman JE, McCabe BF, Huizing EH, Mygind N, eds. Immunobiology, autoimmunity, transplantation in otorhinolaryngology. Amsterdam: Kugler Publications, 1985:11-25.

10. Curran RC, Gregory J. Effects of fixation and processing on immunohistochemical demonstration of immunoglobulin in paraffin sections of tonsil and bone marrow. J Clin Pathol 1980; 33:1047-57.

11. Brandtzaeg P. Tissue preparation methods for immunocytochemistry. In: Bullock GR, Petrusz P, eds. Techniques in immunocytochemistry. Vol 1. London: Academic Press, 1982:1-75.

12. Hsu S, Raine L, Fanger H. Use of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase techniques: a comparison between ABC and unlabeled antibody (PAP) procedures. J Histochem Cytochem 1981;29:577-80.

13. Rathlev T, Hocko JM, Franks GP, Suffin SC, O'Donnell CM, Porter DD. Glucose oxidase immunoenzyme methodology as a substitute for fluorescence microscopy in the clinical laboratory. Clin Chem 1981;27:1513-5.

14. Leduc EH, Avrameas S, Bouteillen M. Ultrastructural localization of antibody in differentiating plasma cells. J Exp Med 1968;127:109-31.

15. Harris JP, Ryan AF. Effect of a middle ear immune response on inner ear antibody levels. Ann Otol Rhinol Laryngol 1985;94:202-6.

16. Paparella MM, Goycoolea MV, Meyerhoff WL. Endolymphatic hydrops and otitis media. Laryngoscope 1979;89:43-58.

17. Hughes GB, Kinney SE, Barna BP, Calabrese LH. Autoimmune Meniere's syndrome. In: Veldman JE, McCabe BF, Huizing EH, Mygind N, eds. Immunobiology, autoimmunity, transplantation in otorhinolaryngology. Amsterdam: Kugler Publications, 1985:119-29.

18. Kumagami H, Nishida H, Dohi K. Experimental labyrinthine lesions through stylomastoid foramen. ORL 1976;38: 334-43.

19. Yoo TJ, Yazawa Y, Tomoda K, Floyd R. Type II collagen-induced autoimmune endolymphatic hydrops in guinea pig. Science 1983;222:65-7.

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ROUND WINDOW MEMBRANE AND PERILYMPH IN EXPERIMENTAL OTITIS MEDIA WITH EFFUSION

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To investigate the influence of middle ear effusion (MEE) on perilymph (PL), an experimental otitis media with effusion (OME) was manufactured in chinchillas by injecting the tympanic cavity with immune complexes. The presence of MEE lasted for up to 9 days after the injection of immune complexes. Perilymph was aspirated on the fourth, tenth, and 21st days after the inoculation. The mean concentrations of albumin, immunoglobulin G, histamine, and prostaglandin E2 (PGE2) were significantly greater in PL from ears with induced OME than in that from normal control ears. The ^{3}H-PGE2 placed on the round window membrane of pathologically affected ears passed into PL in significantly greater amounts than in normal control ears. The findings indicate that the immune complexes placed in the middle ear cavity affect the biochemical milieu of PL, and that MEE is a result of immune complexes.

KEY WORDS — albumin, biochemistry of perilymph, experimental otitis media, histamine, immunoglobulin G, prostaglandins.

INTRODUCTION

Otitis media with effusion (OME) is the most common disease causing conductive hearing loss in young children. The inner ear is an extremely sensitive neurosensory organ buried in the temporal bone and thus protected from mechanical impact and direct invasion by myriad organisms of the environment. The round window membrane (RWM), however, is the only portion that lacks a bony wall between the middle ear and inner ear. Therefore, an inflammatory reaction in the middle ear may cause functional and histologic changes in the inner ear. It is well known that a subtle sensorineural hearing loss is involved in certain forms of OME. Paparella et al[1,2] and Aviel and Ostfeld[3] have demonstrated that sensorineural hearing loss was found in patients with chronic otitis media or OME. Some experimental studies also have demonstrated that middle ear inflammation causes functional and histologic changes in the cochlea.[4-6]

In the present study, we induced immune complex–mediated OME in chinchillas and observed changes in the perilymph (PL) and the RWM in order to note the influence of middle ear effusion (MEE) on the PL.

MATERIALS AND METHODS

Animals. Sixty-two healthy chinchillas (400 to 550 g) were used for this experiment. Seventeen animals were employed for the measurement of immunoglobulin G and albumin (seven animals on day 4, five on day 10, and five on day 21). Fifteen animals were used for measurement of prostaglandin E2 (five animals at each time), and 15 (five at each time) were used for analysis of histamine. For examination of the RWM permeability, 15 chinchillas were used (five at each time). These animals were bred in the animal facility of the Medical College of Oita. Absence of ear infection was confirmed by a fiberscopic observation of the drumhead and by tympanometry. Animals were anesthetized by an intraperitoneal injection of pentobarbital sodium (30 mg/kg) during each collection of samples.

Induction of Immune Complex–Mediated Otitis Media With Effusion. We induced OME by inoculating the chinchillas' tympanic cavities with immune complexes as described in a previous paper.[7] Briefly, immune complexes were prepared by mixing 5 mL of a high titer chinchilla antiserum against keyhole limpet hemocyanin (KLH) — filtered through a 0.22-μm microfilter and incubated at 56°C for 30 minutes to inactivate the complement — with 20 mg of KLH at the optimal ratio. Freeze-dried immune complex was suspended in hydroxypropyl cellulose solution at 0.8% concentration in phosphate-buffered saline. The tympanic cavity of one ear was inoculated with 1 mg of the immune complex in 0.2 mL of the hydroxypropyl cellulose solution through the superior bulla. The inoculation of 1 mg of immune complex was confirmed to develop OME in our preliminary study (Suzuki et al, unpublished data). Middle ear effusion developed within 4 days and disappeared spontaneously 8 or 9 days after the injection. The other ear underwent no treatment and served as a control.

Sample Collection. The PL was aspirated by insertion of a glass capillary tube with a fine tip

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TABLE 1. CONCENTRATION (mg/dL) OF ALBUMIN IN PERILYMPH, SERUM, AND MIDDLE EAR EFFUSION

Time After IC Inoculation	*Animal No.*	*Perilymph*			*Serum (1:100 Dilution)*	*Middle Ear Effusion (1:100 Dilution)*
		OME Side	*Normal Side*	*OME/Normal Ratio*		
Day 4	1	750.0	62.0	12.1	30.0	23.5
	2	235.0	64.0	3.7	22.0	41.0
	3	600.0	47.3	12.7	39.5	44.0
	4	230.0	92.0	2.5	47.5	57.5
	5	700.0	66.0	10.6	67.5	52.5
	6	343.0	103.0	3.4	32.0	53.5
	7	313.0	59.0	5.3	59.0	95.0
	Mean ± SD	453.3 ± 223.4	70.5 ± 19.7	7.19 ± 4.4[a]	42.5 ± 16.4	52.4 ± 21.9
		p<.01				
Day 10	8	152.0	59.0	2.6	33.7	
	9	310.0	150.0	2.1	57.0	
	10	590.0	83.0	7.1	52.5	
	11	175.0	95.0	1.5	52.5	
	12	441.0	80.0	5.5	49.0	
	Mean ± SD	333.6 ± 184.4	93.4 ± 34.2	3.76 ± 2.4	48.9 ± 9.0	
		p<.05				
Day 21	13	205.0	90.0	2.3	38.5	
	14	375.0	174.0	2.2	47.5	
	15	175.0	86.0	2.0	50.0	
	16	300.0	142.0	2.1	36.0	
	17	300.0	107.0	2.8	37.0	
	Mean ± SD	271.0 ± 80.7	119.8 ± 37.6	2.28 ± 0.3[c]	41.8 ± 6.5	
		p<.01				

a>c, p<.05.

IC — immune complex, OME — otitis media with effusion.

through the RWM by use of a micromanipulator after the bulla was opened and the tympanic membrane, incus, and malleus were removed. The RWM was washed with 10 mL of PBS to avoid contamination by MEE. About 20 μL of clear, blood cell-free PL was obtained from each ear. The total amount of PL in chinchillas can be obtained if PL is aspirated carefully and slowly. Blood for serum samples was obtained by a heart puncture. The MEE was aspirated by puncture of the eardrum. Each sample was obtained from the individual animals 4 days, 10 days, and 21 days following the inoculation of immune complex. In sample collection for PGE2 assay, capillary tubes and syringes were coated with indomethacin in ethanol solution.

Measurement of IgG and Albumin. An electroimmunodiffusion (EID) technique was used for this purpose as reported elsewhere.[8] Rabbit antisera to chinchilla albumin were made by immunizing rabbits with purified albumin. The purification of albumin was performed by fractionating chinchilla serum with 50% saturated ammonium sulfate and by disc electrophoresis as described in a previous paper.[8] In the present study, anti-IgG2 was used because the EID technique used in this study required the use of only one subclass; however, antisera to IgG2 reacted with both IgG1 and IgG2. For this reason, the values obtained with this method are interpreted as representing total IgG. Rabbit antisera to chinchilla IgG2 were made by immunizing rabbits with purified IgG2. The IgG2 was obtained from chinchilla serum by ion-exchange chromatography using 0.01 *M* phosphate buffer at pH 7.6 following 50% saturated ammonium sulfate fractionation. To confirm the purity of the fractionated chinchilla albumin and IgG2, immunoelectrophoresis was performed between rabbit antisera to chinchilla whole sera and the chinchilla albumin or IgG2. Only one precipitin band was found.

Determination of Prostaglandin E2. The PGE2 was assayed in PL, serum, and MEE samples by a radioimmunoassay (RIA) using a PGE2 RIA kit (Amersham Japan, Tokyo) according to the method reported by Inagawa.[9] For the assay of PGE2 in PL, the protein elimination procedure was omitted to avoid sample loss because of the small amount of PL sample available for the assay. The effect of protein concentration in the tested sample on the assay of PGE2 was examined. One nanogram of PGE2 was added to chinchilla albumin solutions at the concentrations of 0 mg/100 mL, 300 mg/100 mL, and 750 mg/100 mL, respectively. Each solution was assayed. The results confirmed that the albumin content at such levels insignificantly affects the RIA for PGE2.

Analysis of Histamine. Determination of histamine content in PL, serum, and MEE samples was carried out by the method described by Tsuruta et al.[10] The PL and MEE were diluted 25 and ten times, respectively, with distilled water; and 500 μL of these diluted samples and sera was used for analysis. The extraction of histamine was performed according to the protocol of Tsuruta et al.[10]

TABLE 2. CONCENTRATION (mg/dL) OF IMMUNOGLOBULIN G IN PERILYMPH, SERUM, AND MIDDLE EAR EFFUSION

Time After IC Inoculation	*Animal No.*	*Perilymph* OME Side	*Perilymph* Normal Side	*Perilymph* OME/Normal Ratio	*Serum (1:100 Dilution)*	*Middle Ear Effusion (1:100 Dilution)*
Day 4	1	15.5	3.5	4.4	5.5	6.5
	2	150.0	10.5	14.3	12.0	14.7
	3	172.0	8.6	20.0	14.0	9.2
	4	80.0	12.5	6.4	24.5	19.3
	5	90.0	4.0	22.5	7.5	5.7
	6	40.0	4.6	9.0	4.0	4.5
	7	61.0	9.0	6.8	13.5	11.2
	Mean±SD	87.0±56.6	7.5±3.5	11.9±7.1	11.6±6.9	10.2±5.4
		$p<.01$				
Day 10	8	110.0	10.5	10.5	11.5	
	9	52.5	7.5	7.0	11.0	
	10	32.0	6.0	5.3	11.2	
	11	55.0	7.8	7.1	9.5	
	12	135.0	10.0	13.5	11.5	
	Mean±SD	76.9±43.5	8.4±1.9	8.7±3.3	10.9±0.8	
		$p<.05$				
Day 21	13	60.0	6.3	9.5	18.5	
	14	67.3	7.7	8.7	17.3	
	15	90.0	10.5	8.6	16.7	
	16	80.0	11.5	7.0	23.7	
	17	85.0	22.0	3.9	16.0	
	Mean±SD	76.5±12.5	11.6±6.2	7.5±2.2	18.4±3.1	
		$p<.01$				

IC — immune complex, OME — otitis media with effusion.

After that, the samples were subjected to high speed liquid chromatography-fluorescence analysis.

Permeability of Round Window Membrane to Prostaglandin E2. In order to examine the permeability of the RWM to PGE2, 20 μL of PBS containing ^{3}H-PGE2 (0.002 μCi) (Amersham Japan, Tokyo) was placed on the RWM by use of a microinjector under a surgical microscope. Twenty microliters of ^{3}H-PGE2 solution contained 3.75 μg of PGE2, and the radioactivity was 1,500 counts per minute. This amount of solution can be placed on the RWM without overflow. Thirty minutes later, the PGE2 solution was removed, and the RWM was washed gently and thoroughly with 300 mL of PBS until the radioactivity of the washed solution was not measurable. Then, PL was aspirated and submitted to liquid scintillation spectroscopy.

Histologic Examination. The RWMs were examined by light and electron microscopy. For transmission electron microscopy, the specimens were fixed with Karnovsky's fixative solution (0.2 *M* cacodylate buffer containing glutaraldehyde at 2.5% and paraformaldehyde at 2.0%), postfixed with 2.0% buffered osmium tetroxide solution, and embedded in epoxy resin. Epon-embedded thin sections were stained with uranyl acetate followed by lead citrate.

RESULTS

Albumin and IgG Concentrations. Table 1 shows the results of albumin assays in PL, serum, and MEE samples. The mean value in PL obtained from ears with induced OME was significantly higher than that from normal ears on the fourth day ($p<.01$), tenth day ($p<.05$), and 21st day ($p<.01$) after inoculation of the immune complex, even though the mean concentration and the mean value of the ratio of the OME side versus the normal side gradually decreased after the inoculation of the immune complex. The mean ratio of the OME side versus the normal side on the fourth day significantly exceeded that on the 21st day. The mean values of IgG concentration are given in Table 2. The mean concentration in PL from ears with induced OME was significantly greater than that from normal control ears at each stage ($p<.01$) except on the tenth day. Perhaps because of the small number of samples tested, a statistical significance was not obtained at the stage of the tenth day. In values of IgG concentration in PL obtained from ears with induced OME, there was a great difference between individual animals.

Prostaglandin E2 and Histamine Concentrations. The results are shown in Tables 3 and 4. In PL samples obtained on the fourth day, both mean values for the ear with induced OME were significantly greater ($p<.01$) than those of the normal ears. On the fourth day, the mean concentration of PGE2 in PL samples from ears with induced OME significantly exceeded ($p<.05$) the value on the 21st day. However, these elevations of PGE and the histamine concentrations in PL from ears with induced OME gradually decreased afterward through the

TABLE 3. CONCENTRATION (ng/mL) OF PROSTAGLANDIN E2 IN PERILYMPH, SERUM, AND MIDDLE EAR EFFUSION

Time After IC Inoculation	*Animal No.*	*Perilymph*			*Serum*	*Middle Ear Effusion*
		OME Side	*Normal Side*	*OME/Normal Ratio*		
Day 4	18	1.47	0.043	34.2	0.76	2.78
	19	1.19	0.073	16.3	1.15	2.80
	20	0.96	0.016	60.0	1.03	3.75
	21	1.56	0.058	20.9	1.11	5.40
	22	0.59	0.075	7.9	0.98	4.75
	Mean ± SD	1.15 ± 0.39[a]	0.053 ± 0.02	29.1 ± 20.0	1.01 ± 0.15	3.90 ± 1.17
		p<.01			p<.01	
Day 10	23	0.29	0.021	13.8	1.23	
	24	0.61	0.032	19.1	1.06	
	25	0.16	0.039	4.1	0.81	
	26	0.16	0.013	12.3	2.00	
	27	1.57	0.022	71.4	1.00	
	Mean ± SD	0.56 ± 0.60	0.025 ± 0.01	24.1 ± 27.0	1.22 ± 0.46	
Day 21	28	1.03	0.060	17.2	1.59	
	29	0.44	0.065	6.8	1.10	
	30	0.25	0.020	12.5	0.94	
	31	0.01	0.007	1.4	1.26	
	32	0.07	0.020	3.5	1.27	
	Mean ± SD	0.36 ± 0.41[c]	0.034 ± 0.03	8.28 ± 6.5	1.23 ± 0.24	

a>c, p<.05.

IC — immune complex, OME — otitis media with effusion.

experimental period. Both mean values of MEE were significantly greater ($p<.01$) than those of serum samples.

Passage of Prostaglandin E2 Through Round Window Membrane. The results are given in Table 5. The mean counts per minute of PL samples from ears with induced OME were significantly higher ($p<.01$) than those from normal ears on the fourth and tenth days. The mean value from ears with induced OME exceeded the value from normal ears on the 21st day. However, this difference was not statistically significant. The mean values of counts per minute in ears with induced OME on the tenth and 21st days were significantly reduced, as compared to the mean value on the fourth day. Blood samples taken at each stage showed no radioactivity counts except for background.

Histopathology. Figure 1 shows sections of the inflamed RWM at each stage and a section of a normal ear. On the fourth day, the connective tissue layer was thick, and dilatation of vessels and increased vascularity were evident. Epithelial cells of the outer layer (toward the middle ear) were ap-

TABLE 4. CONCENTRATION (ng/mL) OF HISTAMINE IN PERILYMPH, SERUM, AND MIDDLE EAR EFFUSION

Time After IC Inoculation	*Animal No.*	*Perilymph*			*Serum*	*Middle Ear Effusion*
		OME Side	*Normal Side*	*OME/Normal Ratio*		
Day 4	33	3.7	0.40	9.3	3.7	38.4
	34	2.4	0.38	6.3	4.5	42.1
	35	1.5	0.60	2.5	4.6	50.2
	36	2.7	0.62	4.4	5.9	27.3
	37	5.2	1.44	3.6	4.5	25.5
	Mean ± SD	3.1 ± 1.4	0.69 ± 0.44	5.22 ± 2.7	4.6 ± 0.8	36.7 ± 10.3
		p<.01			p<.01	
Day 10	38	1.4	0.31	4.5	6.0	
	39	1.8	0.45	4.0	5.7	
	40	4.2	1.27	3.3	3.8	
	41	1.3	0.80	1.6	3.5	
	42	0.8	0.54	1.5	4.8	
	Mean ± SD	1.9 ± 1.3	0.67 ± 0.38	2.98 ± 1.4	4.8 ± 1.1	
Day 21	43	1.9	0.50	3.8	5.2	
	44	0.9	0.23	3.9	5.4	
	45	0.5	0.44	1.1	5.1	
	46	0.8	0.61	1.3	6.3	
	47	1.3	0.53	2.5	3.2	
	Mean ± SD	1.1 ± 0.5	0.46 ± 0.14	2.52 ± 1.3	5.0 ± 1.1	

IC — immune complex, OME — otitis media with effusion.

TABLE 5. PASSAGE OF PROSTAGLANDIN E2 THROUGH ROUND WINDOW MEMBRANE

Time After IC Inoculation	*Animal No.*	*Counts Per Minute (%)*	
		OME Side	*Normal Side*
Day 4	48	51 (3.5)	14 (0.97)
	49	61 (4.2)	7 (0.48)
	50	39 (2.7)	0 (0.00)
	51	71 (4.9)	13 (0.90)
	52	56 (3.7)	10 (0.67)
	Mean ± SD	55.6 ± 11.9 (3.80)	8.8 ± 5.6 (0.060)
		p < .01	
Day 10	53	26 (1.8)	9 (0.62)
	54	21 (1.4)	12 (0.83)
	55	37 (1.4)	15 (1.00)
	56	33 (2.4)	20 (1.33)
	57	35 (2.3)	12 (0.80)
	Mean ± SD	30.4 ± 6.7 (2.02)	13.6 ± 4.2 (0.92)
		p < .01	
Day 21	58	34 (2.3)	25 (1.72)
	59	16 (1.1)	17 (1.17)
	60	36 (2.5)	0 (0.00)
	61	36 (2.5)	4 (0.28)
	62	28 (1.8)	9 (0.60)
	Mean ± SD	30.0 ± 8.5 (2.04)	11.0 ± 10.1 (0.75)

Numbers in parentheses indicate what percentage of radioactivity (cpm) of solution containing ^{3}H-PGE2 is represented by perilymph sample.

IC — immune complex, OME — otitis media with effusion.

parently enlarged, as compared to those of normal control ears (Fig 2). However, the tight junctions of these epithelial cells were not loosened. On the tenth and 21st days, the thickness of the RWM increased, and proliferation of fibrocytes and fibroblasts was active. They were enlarged in the subepithelial layer. On the 21st day, fibers increased (Figs 3 and 4). Few neutrophils, macrophages, lymphocytes, or plasma cells infiltrated the inflamed RWM, and none infiltrated the normal RWM. However, basophils occasionally were seen in both normal and inflamed RWMs.

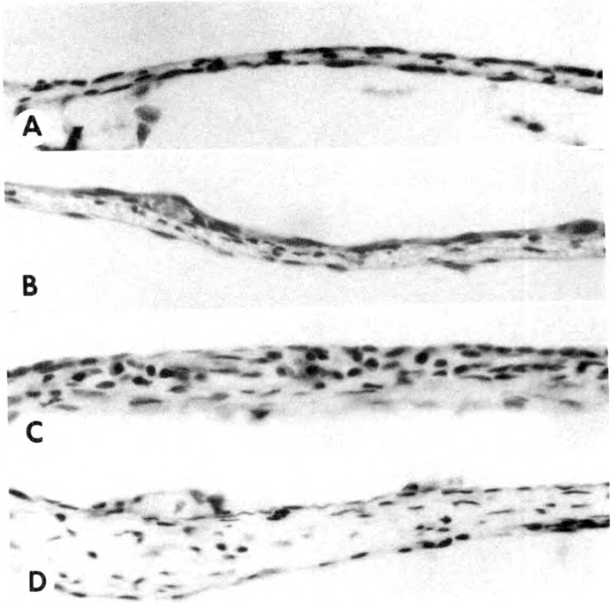

Fig 1. Light micrographs of round window membranes. A) Normal control ear. B-D) Ears with induced otitis media on B) fourth, C) tenth, and D) 21st days.

DISCUSSION

In the present investigation, OME was generated in chinchillas by injecting the tympanic cavity with immune complexes of KLH and anti-KLH chinchilla serum. The induction of experimental OME by this method is highly reproducible, although the presence of MEE lasts for up to 9 days after the inoculation of immune complexes. The characteristics of the immune complex–mediated OME are similar to those of immune-mediated OME that were produced by secondary immune responses of the middle ear.[7] Briefly, infiltrating cells in MEE consist predominantly of macrophages, neutrophils, and lymphocytes. The lining membrane of the tympanic

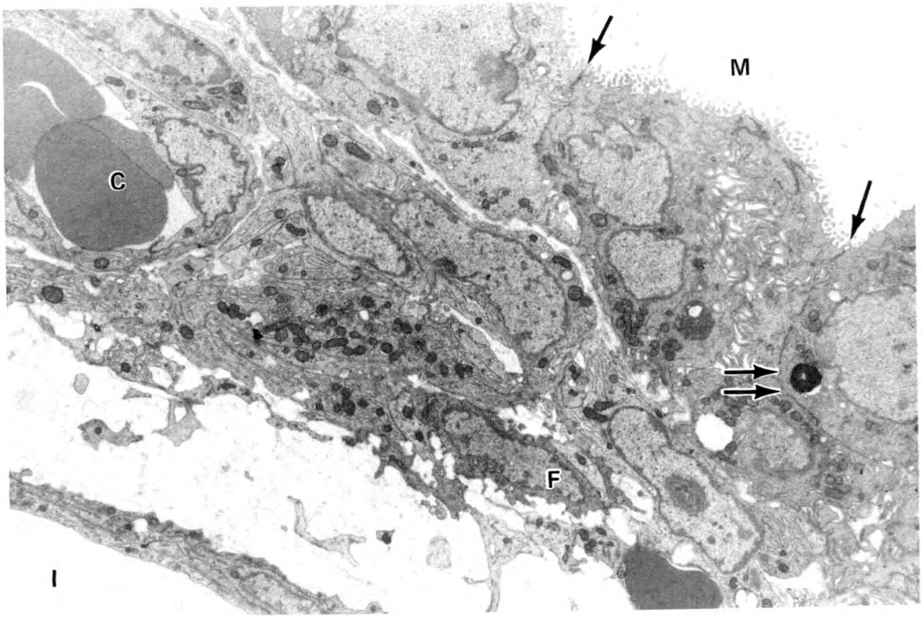

Fig 2. Transmission electron micrograph of pathologically affected ear on fourth day. Epithelial cells are swollen. Cell junctions seem firm. Dilated capillaries are seen in subepithelial layer. M — middle ear side, I — inner ear side, C — capillary, F — fibroblast, single arrows — tight junctions, double arrows — foreign particle that is probably hydroxypropyl cellulose injected into tympanic cavity with immune complex.

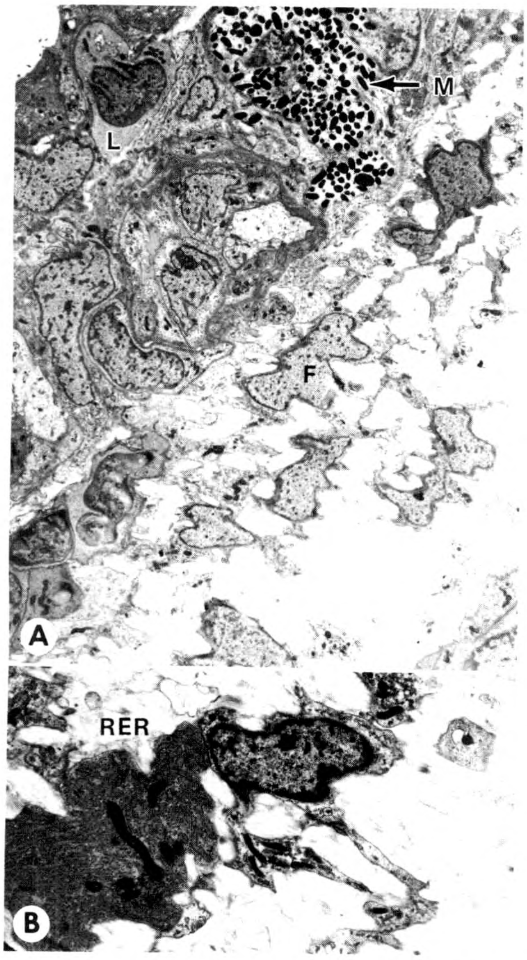

Fig 3. Transmission electron micrograph of pathologically affected ear on tenth day. Proliferation of fibroblasts (F) is active in subepithelial layer. A) Lymphocyte (L) and mast cell (M) are seen in epithelial or subepithelial layer. B) Rough endoplasmic reticulum (RER) of fibroblast is also seen.

cavity becomes thickened. There are abundant neutrophils, lymphocytes, macrophages, and eosinophils in the subepithelial layer. Histamine and PGE2 levels in MEE are significantly high.

The results of this study clearly showed that this type of OME affects the biochemical milieu of PL. The albumin content in PL of ears with induced OME was substantially elevated as compared to that of normal control ears. This elevation continued for 2 weeks after the MEE disappeared, although the level was twice that in the control ears. This was also true of the IgG content. The direct passage of albumin and IgG from MEE to PL through the RWM is the most probable mechanism for the increase in PL of this protein. In fact, the passage of horseradish peroxidase through the RWM into the labyrinth has been reported.[11,12] Goycoolea et al[4] have demonstrated that albumin is permeable to the inner ears through the RWM in cats with experimental OME. Harris and Ryan[5] also have presented data to demonstrate the passage of antibodies from the MEE to the inner ear across the RWM of guinea pigs with immune-mediated OME.

The present study disclosed that relatively high levels of albumin and IgG in PL of ears with induced OME were durable 2 weeks after the disappearance of OME. The most likely explanation of this finding is the relatively long half-life of these serum proteins (20 days). Another possibility is an increased permeability of the perilymphatic blood vessels that facilitates the infiltration of serum proteins to the PL, even through Harris and Ryan[5] denied this possibility. Mogi et al,[8,13] on the other hand, supported the supposition that the main source of immunoglobulins, and albumin as well, in PL is the infiltration from blood vessels surrounding the perilymphatic space.

The results of the histologic observation in this study showed increased vascularity in the RWM of ears with induced OME on the fourth day after the inoculation of immune complexes. This histologic change was still apparent after the disappearance of MEE. This evidence might suggest an accelerating infiltration of serum proteins into the PL, at least at the site of the RWM, after the MEE has disappeared, even though detachment of endothelial cell junctions was not clearly found in this study. On the fourth day, the epithelial cells of the outer layer were swollen, and cell junctions seemed firm. Goycoolea et al[4] mentioned the possibility of alteration of the cell junctions, but it could not be found in this study. It should be considered nevertheless that hypervascularity of the RWM suggests an accelerating infiltration of serum proteins into PL. Electron microscopic observations revealed foreign particles in the epithelial and subepithelial layers of the pathologically affected RWM. The foreign particles probably were hydroxypropyl cellulose particles injected into the tympanic cavity with the immune complexes. It is considered that cellulose particles were absorbed into the RWM by the mechanism of endocytosis of the epithelial cells. The evidence suggests the possibility that macromolecular proteins such as albumin and IgG may pass through the RWM to PL by this mechanism. Although the passage of hydroxypropyl cellulose into the RWM suggests that immune complexes might be transported into the RWM, the presence of immune complexes in PL was not investigated in this study. It is possible that these immune complexes may induce local inflammation in the RWM and perilymphatic space. However, in our present study, the inflammatory cell infiltration was seen to some extent in the RWM, but not in the perilymphatic space.

Prostaglandins are one of the metabolites of arachidonic acid, serving an important regulatory function. Bernstein et al[14] reported that prostaglandins are present in MEE of humans in greater amounts than in the corresponding sera. In both our previous[7] and present studies of chinchillas, it was found that the mean PGE2 level in the MEE is sig-

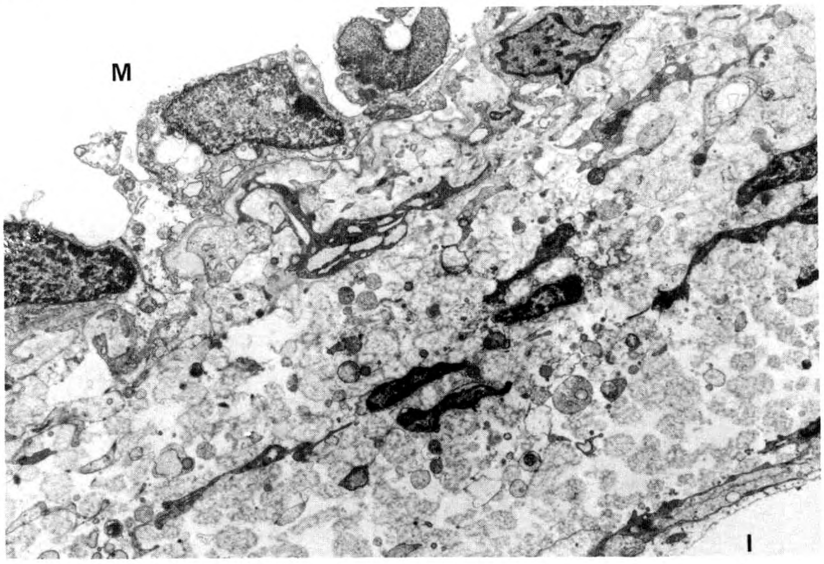

Fig 4. Transmission electron micrograph of pathologically affected ear on 21st day shows increased fibers in subepithelial layer. M — middle ear side, I — inner ear side.

nificantly higher than that in the corresponding sera. Since prostaglandins are manufactured in all cells other than red blood cells, even though different cell types show marked variation in the amounts, PGE2 in the MEE comes chiefly from the infiltrating cells in the MEE and inflamed middle ear mucosal cells. We found, in this study, an extremely elevated PGE2 level for each PL sample obtained from ears with induced OME on the fourth day. The mean PGE2 level in PL of the diseased ears (fourth day) was 29 times greater than that of the normal control ears. The results of the tracer experiment of ^{3}H-PGE2 in the present study showed, without a doubt, that PGE2 placed on the pathologically affected RWM passes into the PL. In this OME model, the complement system might be activated by immune complexes. The breakdown products of complements 3 and 5 (C3a and C5a) are anaphylatoxins, releasing chemical mediators containing histamine from mast cells. It was demonstrated that the histamine content in MEE was greater than that in the corresponding sera. On the fourth day, when MEE was observed, the histamine level in PL of ears with induced OME significantly exceeded that of normal ears. The histamine detected in PL might be derived from MEE, and possibly is produced and released by mast cells in the connective tissue of the RWM. Since prostaglandins and histamine are mediators of inflammation, these findings imply that OME may affect the PL. However, the extent of the influence on the PL apparently depends on the severity and duration of the OME.

The present study, as well as studies by Goycoolea et al[4] and Harris and Ryan,[5] failed to find histopathologic changes in the perilymphatic space and other inner ear compartments of ears with induced OME. These studies did not evaluate the inner ear function. Morizono et al[6] demonstrated in their electrophysiologic study that evidence of sensorineural hearing loss was found in chinchillas with induced pneumococcal OME (purulent type).

In conclusion, the findings of the present study demonstrated that OME affects the biochemical milieu of PL. In a future study in this laboratory, an electrophysiologic investigation will be employed to detect also the effect of OME on the inner ear function.

REFERENCES

1. Paparella MM, Brady DR, Hoel R. Sensorineural hearing loss in chronic otitis media and mastoiditis. Trans Am Acad Ophthalmol Otolaryngol 1970;74:108-15.

2. Paparella MM, Oda M, Hiraide F, Brady D. Pathology of sensorineural hearing loss in otitis media. Ann Otol Rhinol Laryngol 1972;81:632-47.

3. Aviel A, Ostfeld E. Acquired irreversible sensorineural hearing loss associated with otitis media with effusion. Am J Otolaryngol 1982;3:217-22.

4. Goycoolea MV, Paparella MM, Goldberg B, Carpenter A-M. Permeability of the round window membrane in otitis media. Arch Otolaryngol 1980;106:430-3.

5. Harris JP, Ryan AF. Effect of a middle ear immune response on inner ear antibody levels. Ann Otol Rhinol Laryngol 1985;94:202-6.

6. Morizono T, Giebink GS, Paparella MM, Sikora MA, Shea D. Sensorineural hearing loss in experimental purulent otitis media due to *Streptococcus pneumoniae*. Arch Otolaryngol 1985;111:794-8.

7. Suzuki M, Kawauchi H, Mogi G. Immune-mediated otitis media with effusion. Am J Otolaryngol 1988;9:199-209.

8. Mogi G, Lim DJ, Watanabe N. Immunologic study on the inner ear. Immunoglobulins in perilymph. Arch Otolaryngol 1982;108:270-5.

9. Inagawa T. Assay of prostaglandin E. J Med Technol (Jpn) 1982;26:135-47.

10. Tsuruta Y, Kohashi K, Ohkura Y. Determination of histamine in plasma by high speed liquid chromatography. J Chromatogr 1978;146:490-3.

11. Rhodes T. Round window membrane permeability of horseradish peroxidase: an electron-microscopy study [Thesis]. Minneapolis: University of Minnesota, 1980.

12. Saijo S, Kimura RS. Distribution of HRP in the inner ear after injection into the middle ear cavity. Acta Otolaryngol (Stockh) 1984;97:593-610.

13. Mogi G, Kawauchi H, Suzuki M, Sato N. Inner ear immunology. Am J Otolaryngol 1985;6:142-7.

14. Bernstein JM, Okazaki T, Reisman RE. Prostaglandins in middle ear effusions. Arch Otolaryngol 1976;102:257-8.

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SOFT TISSUE SURGERY WORKSHOP

The Cleveland Clinic Foundation is sponsoring a continuing education program entitled Soft Tissue Surgery Workshop, to be held February 1-2, 1990, at The Clinic Center Hotel in Cleveland. For further information, contact The Cleveland Clinic Education Foundation, Department of Continuing Education, 9500 Euclid Avenue, TT31, Cleveland, OH 44195-5241; 444-5696 (local), (800) 762-8172 (Ohio), (800) 762-8173 (outside Ohio).

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RECENT ADVANCES IN VESTIBULAR TESTING AND REHABILITATION

The Cleveland Clinic Foundation is sponsoring a continuing education program entitled Recent Advances in Vestibular Testing and Rehabilitation, to be held April 24-25, 1990, at the Stouffer Tower City Plaza Hotel in Cleveland. For further information, contact The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Avenue, TT31, Cleveland, OH 44195-5241; 444-5696 (local), (800) 762-8172 (Ohio), (800) 762-8173 (outside Ohio).

Ann Otol Rhinol Laryngol 98:1989

IMAGING CASE STUDY OF THE MONTH

MAXILLARY SINUS NEOPLASM

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INTRODUCTION

Computed tomography is used extensively in the diagnosis of maxillary sinus cancer. This modality clearly defines bone erosion when present. Depending on the location and extent of a maxillary sinus tumor, CT may show opacity of surrounding sinuses. Magnetic resonance is the best imaging technique to differentiate between obstructive opacity and invasion suspected on the CT study, as illustrated by the following patient.

The patient is a 45-year-old woman with a 3-month history of left-sided nasal obstruction. She noticed difficulty breathing through her left nostril and assumed it was secondary to nasal congestion. This was treated with decongestants and antibiotics with no decrease in her symptoms. She sought medical attention following the onset of left ear pain and left-sided headaches of increasing severity. The physical examination showed a polypoid mass in the left naris. A biopsy revealed squamous cell carcinoma clinically staged as a T4N0M0 tumor.

A CT coronal view (Fig 1A) shows left maxillary sinus opacity with erosion along the lower anterior surface and in the region of the upper nasal surface of the sinus. The left naris is opaque, and the orbital floor and ethmoid-maxillary septum are absent. The left ethmoid sinus is opaque. A midmaxillary axial view (Fig 1B) better demonstrates erosion of the left maxillary nasal surface. The left frontal sinus was opaque on other views (not illustrated).

Anterior (Fig 2A) and posterior (Fig 2B) T2 MR coronal images through the maxillary, nasal, and ethmoid plane show that the signal intensity of the tumor is less than the intensity of signal produced by obstructive secretions in the left ethmoid sinus. These images also show no evidence of anterior fossa involvement.

Orbit studies also were obtained by MRI. Figure 3A is a coronal retrobulbar T1 image. It shows ex-

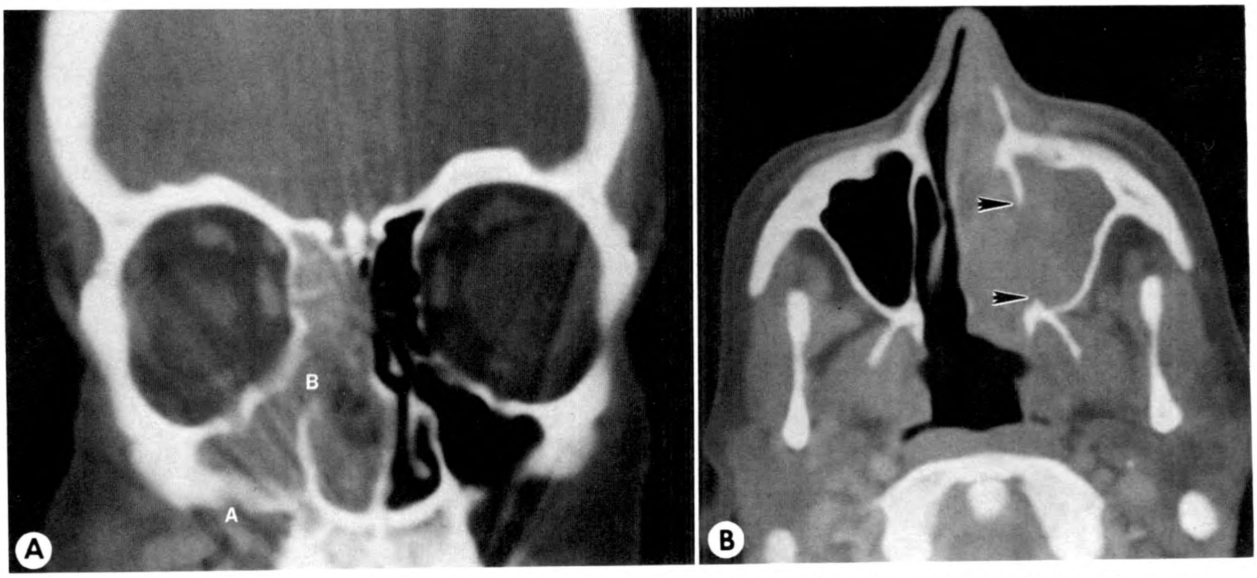

Fig 1. Sinus computed tomographs. A) Midmaxillary coronal view showing left maxillary, left nasal, and left ethmoid opacity. A — anterior maxillary erosion, B — nasal wall erosion. B) Axial midmaxillary view with left maxillary sinus and left naris opacity. Nasal wall erosion lies between arrowheads.

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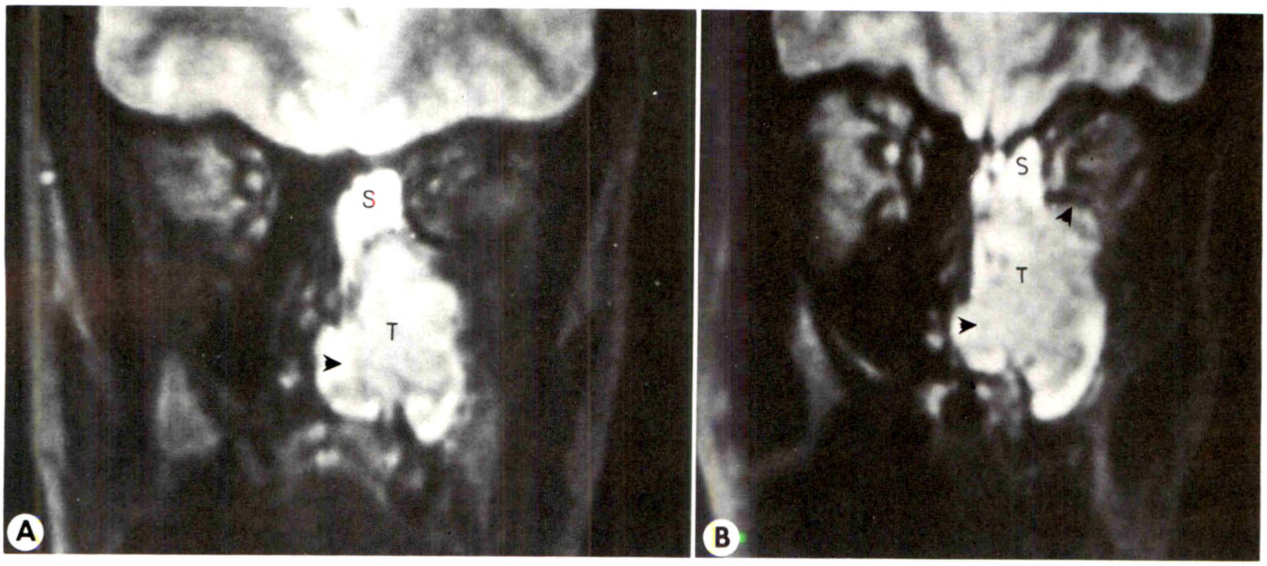

Fig 2. Sinus T2 magnetic resonance images. A) Anterior maxillary view with low-signal tumor (T). Secretions fill ethmoid sinus cell (S). Arrowhead — intranasal tumor extension. B) Posterior maxillary view showing tumor (T), ethmoid secretions (S), orbital invasion (upper arrowhead), and nasal invasion (lower arrowhead).

tension of the left maxillary tumor through the orbit floor into the area of the inferior rectus muscle. Similarly, the lower border of the medial rectus muscle also is invaded by tumor. These changes are reflected by the absence of high-signal fat surrounding the lower borders of these muscles. Figure 3B is a T2 axial MR image at the level of the optic nerve. The bright signal produced by water in the ethmoid and sphenoid sinus cells reflects the presence of secretions in these cells.

DISCUSSION

During the late 1970s and early 1980s, CT became important in the evaluation of paranasal sinus tumors. This examination modality has been used to delineate tumor erosion into the orbit, base of skull, oral and nasal cavities and other sinuses, surrounding soft tissue, and bony structures.[1]

The major limiting factor of CT imaging is the poor differentiation between occluded or inflamed sinus cavities and adjacent tumor.[2] This lack of differentiation may mislead the surgeon in the determination of a safe resection margin.[3,4]

More recently, MRI has arisen as a major advance in differentiating adjacent soft tissue structures of different composition.[5,6]

The T1 MR images depend primarily on very

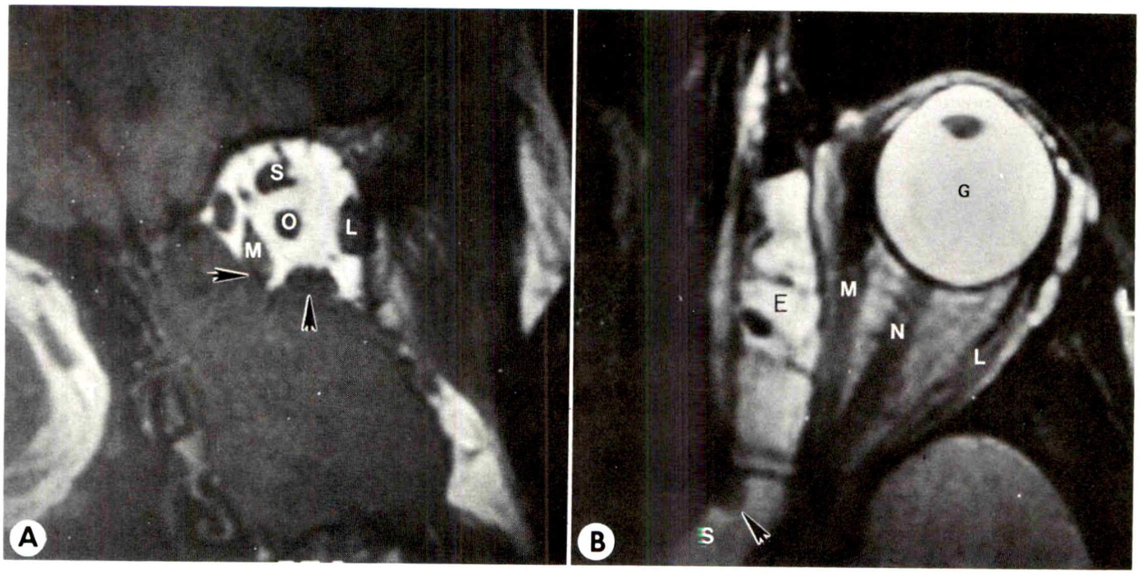

Fig 3. Orbital magnetic resonance images. M — medial rectus muscle, L — lateral rectus muscle. A) T1 oblique (perpendicular to optic nerve) retrobulbar image. T — tumor, S — superior rectus muscle, O — optic nerve, vertical arrow — tumor extending into inferior rectus muscle, horizontal arrow — tumor invading inferior portion of medial rectus muscle. B) T2 axial image of left orbit in optic nerve plane. G — globe, N — optic nerve, E — ethmoid sinus, S — sphenoid sinus with small tumor nodule at arrowhead.

mobile hydrogen protons contained in fat or fatlike substances to produce the brightest signal intensity. Figure 3A illustrates the absence of expected fat signal as the indication of tumor invasion.

The bright signal of a T2 MR image is produced by the less mobile hydrogen protons of water. The obstructive secretions in Fig 2A,B are indicated by their signal intensity, which is brighter than that of the tumor in these views. Similarly, the bright signal in the ethmoid sinus depicted by Fig 3B indicates the presence of secretions rather than tumor. Note also how brightly the vitreous water signal in the globe is depicted in this view.

The hydrogen protons in bone are much less mobile and fewer in number than in tissue or fluid. Bone areas, therefore, are black or signal-free in the usual MRI studies. This is well seen in Fig 3B, in which the delicate ethmoid septae produce thin black lines between the secretion-filled ethmoid cells. Those familiar with MRI usually can determine bone integrity on conventional MRI studies. Magnetic resonance may be used as the principal imaging technique in evaluating tumors similar to that in our patient.

The patient underwent a radical maxillectomy with orbital exenteration. The surgical findings correlate well with the MRI results. Since the anterior fossa, base of the skull, and upper ethmoid air cells were not invaded, as demonstrated by the MRI scan, we were able to resect that tumor with surrounding safe margins. The imaging precision of the MRI scan provided information that negated the need for a more extensive surgical procedure.

REFERENCES

1. Bilaniuk LT, Zimmerman RA. Computed tomography in evaluation of the paranasal sinuses. Radiol Clin North Am 1982; 20:51-61.

2. Hasso AN. CT of tumors and tumor-like conditions of the paranasal sinuses. Radiol Clin North Am 1984;22:119-30.

3. Som PM, Lawson W, Biller HF, Lanzieri CF. Ethmoid sinus disease: CT evaluation in 400 cases. Part I. Nonsurgical patients. Radiology 1986;159:591-7.

4. Som PM, Lawson W, Biller HF, Lanzieri CF. Ethmoid sinus disease: CT evaluation in 400 cases. Part II. Postoperative findings. Radiology 1986;159:599-604.

5. Dillon WP. Magnetic resonance imaging of head and neck tumors. Cardiovasc Intervent Radiol 1986;8:275-82.

6. Dillon WP. Applications of magnetic resonance imaging to the head and neck. Semin Ultrasound CT MR 1986;7:202-15.

THE INTERNATIONAL SYMPOSIUM ON CLINICAL AND BASIC OTOLOGY

The International Symposium on Clinical and Basic Otology will be held June 4-6, 1990, in Beijing, People's Republic of China. The abstract deadline is December 31, 1989. For further information, contact the Beijing Institute of Otorhinolaryngology, Chan Liu, MD, Professor and Director, 17 Hougou Lane, Beijing 1000005, People's Republic of China.

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PATHOLOGY CONSULTATION

DERMAL ECCRINE CYLINDROMA

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Certain dermal appendage tumors have a striking histologic and clinical homology with some tumors arising from the salivary duct system. The dermal eccrine cylindroma is an exemplar. Arising from the eccrine ducts, this neoplasm is only occasionally found outside the head and neck, has a recurrence rate of over 40%, and in its malignant form is a high-grade carcinoma. Its counterpart in salivary glands, the dermal analogue tumor, manifests a histologic similarity, if not identity, also has a relatively high recurrence rate, and can also undergo malignant change.

The dermal eccrine cylindroma is an adenexal tumor of skin that holds special interest for the head and neck surgeon. The majority (90%) arise as small, usually solitary, slow-growing lesions on the head and neck; occasionally they arise as spectacular giant forms known as turban tumors because of the disfigurement they produce.[1] There is a histologically homologous tumor of the major salivary glands, preponderantly the parotid gland, that may exist independently or be part of a cutaneous-salivary syndrome.[2-4] In either skin or salivary sites, the lesion may be mistaken for an adenoid cystic carcinoma.

Familial multiple dermal cylindromas are inherited as an autosomal dominant trait.[5] Multiple tumors may also be associated with other skin tumors, trichoepitheliomas, eccrine spiradenomas, and cylindromas with features of both of these or syringoma. Solitary forms do not show a familial tendency. There is a 10:1 female predominance.[1,5] Clinical presentation occurs over a wide time period from early childhood to the eighth decade.

Although the histogenesis of the dermal eccrine cylindroma continues to be debated, histologic, ultrastructural, and immunocytochemical studies indicate origin from the intradermal coiled duct region of the eccrine sweat gland.[5]

The scalp (including the hairline) and other areas of the head and neck account for 90% of the reported sites of dermal eccrine cylindromas. Only a small number of patients with tumors on the trunk or extremities do not also have tumors involving the scalp.[1] The ear, including the external auditory canal, accounts for approximately 6% of the reported tumors.[1]

The lesions are nodular, firm, and pink-red. Unless coalesced in clusters, they average 1 cm in diameter.

The cylindroma is an unencapsulated, upper dermal lesion usually separated from the overlying epidermis (see Figure, A). Crain and Helwig[1] stressed the three essential histologic features: cords of basaloid cells, hyaline material, and cystic and/or solid cell masses with ductlike structures. The architectural growth pattern is lobular and mosaic in appearance with cords, islands, and nodules (see Figure, B). In some areas, hyaline outlines the configuration of lobules and islands; in others, the hyaline material is in a droplet form between individual cells or in irregular masses (see Figure; C,D). Perivascular hyaline cuffing may also be a prominent feature. Because of isolated islands and lack of encapsulation separate from the main tumor, an infiltrative quality is often imparted.

The hyalinized material contiguous to the tumor cell clusters is composed not only of basement membrane components, but also of other connective tissue constituents, ie, type I and type III collagen and fibronectin.[6]

Recurrence after excision of a dermal eccrine cylindroma is quite common. In the series reported by Crain and Helwig[1] it was 42%. Fifty percent of these were within 3 years of the primary excision. Multinodularity and multifocal growth are held responsible, as they also are for the salivary gland counterparts.[3,4]

The frequency of carcinoma arising from a dermal cylindroma is unknown. Cooper et al[7] estimate that at least 14 cases have been reported. The majority of these arose in patients with multiple (turban tumor) cylindromas of the scalp and were evinced by a rapid enlargement of a part of the maternal lesion. The carcinomas often retained features evocative of the cylindroma; others lacked that identity. In their 10 patients with follow-up, the lethality of the carcinoma is shown. Five patients died of disseminated disease, and three from local, uncontrolled aggression.

The dermal analogue monomorphic adenoma of

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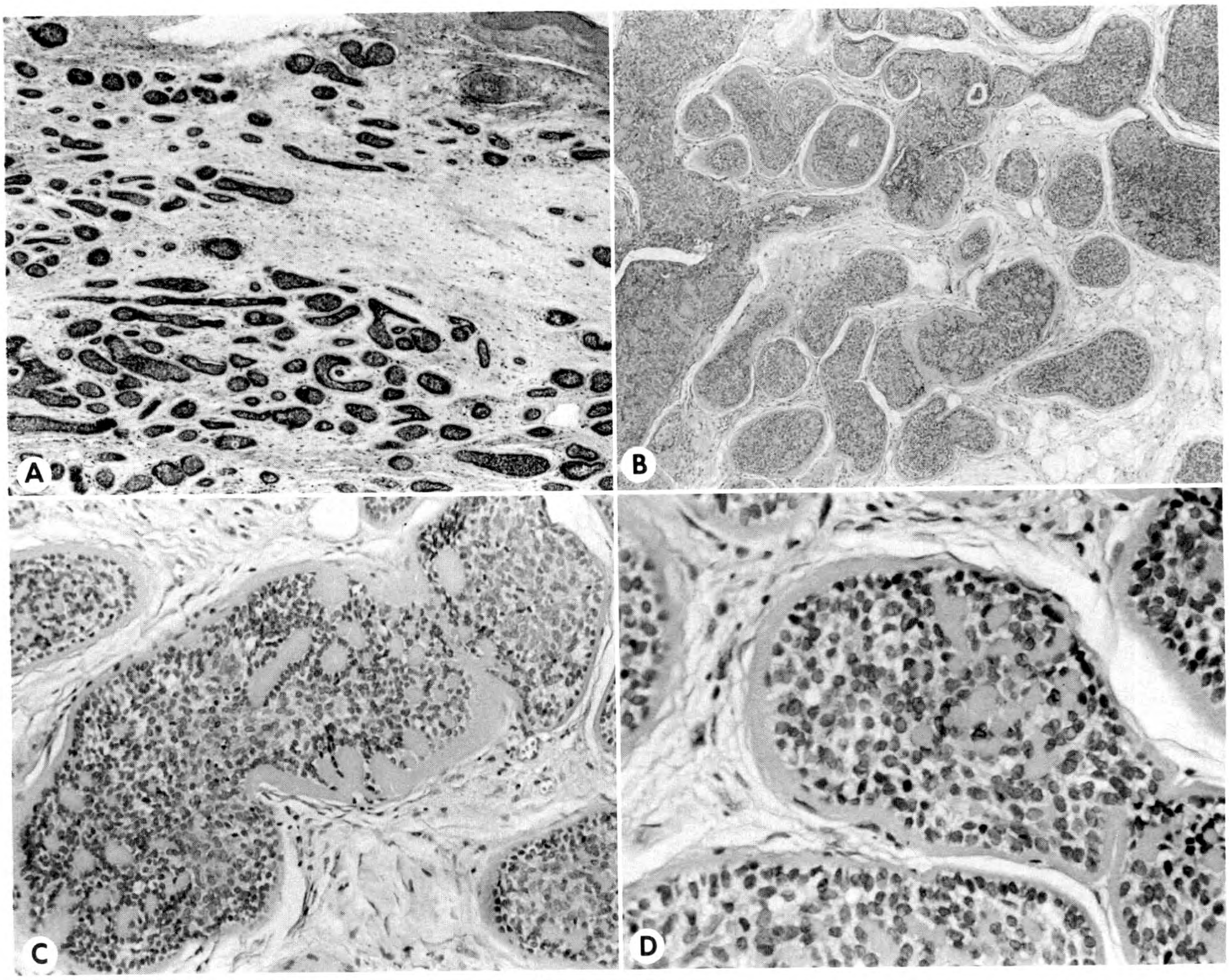
REPRINTS — John G. Batsakis, MD, Division of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.



Dermal eccrine cylindroma. A) Of skin of temple (H & E, original x40). Isolated epithelial islands infiltrate dermis. B) Of skin of external auditory canal (H & E, original x80). Mosaic growth pattern is evident. C) Eosinophilic basement membrane material surrounds islands and is deposited within cell masses (H & E, original x160). D) Basaloid cells, lobular growth, hyaline droplets, and circumscribing sheaths about epithelial islands (H & E, original x220).

salivary glands is histologically indistinguishable from a dermal eccrine cylindroma.[2,3] Its recurrence rate is also similar. Our experience with carcinomas ex monomorphic adenoma is that the dermal analogue tumor is also more likely to undergo malignant changes than other monomorphic adenomas. In follow-up periods up to 9 years, none of our six patients with malignant dermal analogue tumors have had metastases, but characteristically, they have had multiple recurrences. As with the malignant dermal cylindroma, a rapid growth of atypical basaloid cells with necrosis and mitoses and retention of architectural features of the benign precursor is found.

REFERENCES

1. Crain RC, Helwig EB. Dermal cylindroma (dermal eccrine cylindroma). Am J Clin Pathol 1961;35:505-15.

2. Batsakis JG, Brannon RB. Dermal analogue tumours of major salivary glands. J Laryngol Otol 1981;95:155-64.

3. Batsakis JG, Brannon RB, Sciubba JJ. Monomorphic adenomas of major salivary glands: a histologic study of 96 tumours. Clin Otolaryngol 1981;6:129-43.

4. Headington JT, Batsakis JG, Beals TF, Campbell TE, Simmons JL, Stone WD. Membranous basal cell adenoma of parotid gland, dermal cylindromas, and trichoepitheliomas. Cancer 1977;39:2460-9.

5. Cotton DWK, Braye SG. Dermal cylindromas originate from the eccrine sweat gland. Br J Dermatol 1984;111:53-61.

6. Weber L, Wick G, Gebhart W, Krieg T, Timpl R. Basement membrane components outline the tumour islands in cylindroma. Br J Dermatol 1984;111:45-51.

7. Cooper PH, Frierson HF, Morrison AG. Malignant transformation of eccrine spiradenoma. Arch Dermatol 1985;121:1445-8.

BOOK REVIEWS

Scott-Brown's Otolaryngology

Alan G. Kerr, series ed. 5th ed. Vols 1-6. Hard cover, illustrated, indexed, 1987. Butterworth Publishers, Boston, $595.

The addition of volumes on pediatric otolaryngology and adult audiology increases the number of volumes in this set from the original two (published in 1952) to six volumes in this fifth edition. In the ensuing 35 years, Scott-Brown's reputation as the mastermind and editor of the first postwar British text on otolaryngology, indeed the bible of British otolaryngology, was perpetuated until his death in 1987. His disciples preserve his recognition and acclaim in this syllabus, which has been prepared by authors who are resolute in the coverage of their topic. Rarely will the reader of any of the volumes (on basic sciences, adult audiology, otology, rhinology, laryngology, and pediatric otolaryngology) be confronted by skepticism or tenuous information. Perhaps such aggressive coverage of clinical management precludes more than a brief discussion of readily available and widely accepted diagnostic procedures, such as rotational and platform testing for the vertiginous patient. Although the lack of in-depth coverage of such modalities appears to be a striking omission, it must be realized that the fluidity of the practice of otorhinolaryngology today makes it almost impossible to maintain the up-to-date integrity of a text through the date of publication. Generally, the contributors have supplied their readers with a generous bibliography, should additional information be desired.

Each chapter is well written, stimulating, and complemented by most useful drawings and photographs. Although the drawings are simple, they fulfill all didactic requirements. Where differences in opinion are expressed in the literature (adenoidectomy, endolymphatic shunt, etc), the reader is not subjected to persuasion. Instead, the different philosophies are presented and the reader is directed to appropriate references for further insight into the controversies.

As a reference source, particularly in the art of history-taking and the physical examination, these volumes are recommended enthusiastically. The entire set is unique in presenting usable, dependable, and easily understood information that can be applied quickly to the practice of otolaryngology. Specific topics may be followed easily through the index. However, the overall quality of the contributions, well presented with minimal deficiencies, encourages full reading of each chapter.

This introduction is valid for each of the six volumes in this set; therefore, only significant characteristics will be noted for each volume.

DENNIS G. PAPPAS, MD
Birmingham, Alabama

Vol 1. Basic Science, David Wright, ed

The presentation and discussion of the basic science of the head and neck in this volume is as good as its compeers. Some of the chapters have been "combined and refined" from the fourth edition. However, this remarkable assemblage includes several new topics, including laser surgery and the physiologic aspects of wound healing, biomaterials, anatomy and ultrastructure of the human ear, physiology of the ear, perception of sound, and basic immunology.

Particularly noteworthy is the excellent discourse on the physiology of the hearing mechanism, which is accompanied by superior and uncommon illustrations. This is a well-integrated section that provides a good review of recent scientific progress.

The reader will gain excellent insight into the basic science of immunology from this easily understood text. However, it is disturbing that application of immunology specifically to otolaryngology is not addressed, and the literature is not reviewed. There is also a lack of in-depth discussion of magnetic resonance imaging technique (such as the characteristics of the physical and chemical properties that permit T-weighted images to compare and, possibly, diagnose different lesions).

Nevertheless, the fresh insights and original formulations provided in this volume must be appreciated.

DENNIS G. PAPPAS, MD
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Vol 2. Adult Audiology, Dafydd Stephens, ed

Audiologic medicine is a nonsurgical medical specialty that apparently has emerged in many parts of Europe. However, this concept has not been promoted in the United States. This philosophic difference may explain the discrepancy in the useful application of this volume, depending on the reader's (especially audiologist's) education and experience. Its very broad scope and depth of coverage hinder its practical use by otolaryngologists dealing with audiologic problems, and by clinical audiologists. Indeed, some chapters are so technical and "formula-filled" that they would be of minimum value to anyone other than a research audiologist or hearing scientist. A result of this vast amount of mathematic, technical, and scientific information is often slow and laborious reading. Nevertheless, most of the text is written in a lucid and understandable manner. For the most part, the material is organized in a logical sequence, one exception being the chapter Computers in Audiology interjected between Acoustics and Electroacoustics and Epidemiology of Hearing Disorders.

The chapters Hearing Aids and The Role of the Cochlear Implant are particularly well written and informative. An excellent section, Noise and the Ear, covers the gamut of malefactors, including fireworks, classical music, and dental drills. On the other hand, the chapter Legal and Ethical Matters, although interesting, will be of minimum usefulness to anyone other than physicians in Britain. The only significant topic lacking in this volume was omitted intentionally. The practice of audiology and the impact of hearing impairment as they relate to children are not addressed. Justification for this is that this information is included in the volume Paediatric Otolaryngology (vol 6).

Depending on the reader's field of expertise (research, medicine, or clinical audiology), this volume may be considered a wealth of useful information or a text that includes extraneous and irrelevant data along with pertinent information. In any case, the reference citations at the end of each chapter, good volume indexes, and a cumulative index of all six volumes make this set of value as a source of reference. In addition, the contributors probably have succeeded in providing an overview of "audiological medicine," under the misleading title of Adult Audiology.

J. KEITH LOWRY, MS, CCC-A
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Vol 3. Otology, John B. Booth, ed

Several chapters in this volume stand out because of their completeness and lucidity. The coverage of sudden and fluctuant sensorineural hearing loss is an excellent introduction of the neophyte to these maladies, and offers a most comprehensive review of the literature regarding them. The discussion of sensorineural hearing loss of undiagnosable vascular origin is superb. Indeed, this chapter may be the most valuable part of this volume, although the chapters on otosclerosis, Meniere's disease, and ototoxicity are exemplary.

The vestibular system is divided into two chapters, on pathology and vertigo. The conspicuous deficit in coverage is in the area of the diagnostic workup. Since electronystagmography, rotational testing, and platform testing are not discussed, details of other diagnostic procedures (Dix-Hallpike, minimal caloric tests, hyperventilation, headshake tests, the use of Frenzel glasses, etc) would have made a useful addition.

Although meatography with air contrast rarely is indicated today for detection of small internal auditory meatus tumors, the author advocates this procedure over magnetic resonance imaging. Nevertheless, the latter procedure, which is currently used for this purpose in most otologic clinics, is discussed throughout this volume.

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Vol 4. Rhinology, Ian S. Mackay and T. R. Bull, eds

In this fifth edition, the editors have added chapters on endoscopy of the nose and sinuses, rhinomanometry, the mechanisms and treatment of allergy, sleep apnea and snoring, and the orbit. Overviews of testing the sense of smell, septal ulceration and perforations, and septal surgery are covered adequately and with good instructions.

Presentation of the use of computed tomography in diagnosing paranasal sinus disease is well done. However, the expense and time involved in CT scanning limits its use to problem cases, or those in which neoplasm is suspected (distinction made by author). Conventional plain-film x-rays, which are not discussed, continue to be the primary radiographic procedure, although they are limited in the investigation of paranasal sinus disease.

On rare occasions, it is difficult to grasp the authors' description of disease entities. Temporal arteritis is a cause of headache and facial pain, yet scant insight into this significant condition is given; actually, a bit more information about it is given in the discussion of otalgia in the volume on otology. Nevertheless, temporal arteritis is listed in the cumulative index and can be found in both volumes.

Dennis G. Pappas, MD
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Vol 5. Laryngology, P. M. Stell, ed

The overview of endoscopic and surgical procedures presented in this volume is most appropriate for the neophyte. However, the more experienced head and neck surgeon might welcome and benefit from the opportunity it provides to review philosophies in the management of such conditions as vocal cord reinnervations, bilateral adductor pharyngeal paralysis, Teflon injections, and benign mesodermal tumors.

Although current techniques such as laser and microendoscopy are mentioned, no elaboration on their application is presented. The author does, however, stress the use of head mirrors (a seemingly lost art among new otolaryngologists). He also presents a good review of flexible nasopharyngolaryngoscopy, as well as pathologies of the mouth, particularly those seen in common conditions like obstructive sleep apnea. Helpful clarification of the characteristics of oral candidiasis in the young male and hairy leukoplakia is provided. Human immunodeficiency virus, the producer of acquired immunodeficiency syndrome (AIDS), is discussed in a concise and well-written half-page. However, since 40% of the patients with AIDS manifest otolaryngologic symptoms, it might have been prudent to extend this discussion to cover epidemiology, etiology, immunology, pathology, clinical manifestations, treatment, and prevention. It is hoped that this subject will be extended to cover these areas in the next edition. On the other hand, "old" diseases (eg, tuberculosis, scleroma, and syphilis), which are discussed in at least three other volumes in the set, have pages allocated to them.

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Vol 6. Paediatric Otolaryngology, John N. G. Evans, ed

The first five chapters of this volume diagram the causes of hearing loss in both nonsyndrome (congenital) and syndrome patients. There are several "coined" findings, such as the mastoid being typically unpneumatized and the attic and antrum often reduced to slitlike proportions in Treacher Collins syndrome. Otologic findings (including radiographic) in many conditions are presented concisely. Even so, some known ones are omitted, such as fixation of the stapedial footplate in Marfan's syndrome (". . . deafness is a rare finding" [36]).

The section on testing and screening of the hearing is followed by two excellent chapters in which speech and language disorders are defined clearly according to the most recent available research. Issues related to diagnosis and treatment of these disorders are addressed in a manner appropriate for the physician who might require assistance in determining the need to refer a patient to a speech-language pathologist.

Although there are not many studies on children with vestibular problems, the literature on this problem is reviewed completely. Craniofacial abnormalities again appear (in two chapters). It would seem that these could have been organized into the primary hearing chapters, thus not giving the appearance of a mélange. Coverage of mainstream head and neck, pharyngeal, and laryngeal medicine is generally good, with no cause for dissent.

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Microsurgery of the Skull Base

Ugo P. Fisch and Douglas Mattox. Hard cover, illustrated, indexed, 669 pages, 1988. Thieme Stuttgart, New York, $168.

This large atlas describes all modern surgical procedures on the skull base. Its aim is to show the details of each surgical procedure so that the interested surgeon may perform it. It is divided into ten chapters, and each chapter is divided into seven parts: 1) general considerations, consisting of indications, contraindications, preoperative preparations, instrumentation, postoperative care, and complications; 2) surgical anatomy; 3) surgical technique, describing the operations step by step from the skin incision to skin closure, with many schematic drawings; 4) applications of the principal operation on different diseases and pathologic conditions with specific modification of the principal operation to the specific condition (eg, in Chapter 1, modifications of subtotal petrosectomy in cholesteatoma, fractures of the temporal bone, CSF leak, facial palsy); 5) postoperative tips and pitfalls; 6) imaging of several illustrative cases of the diseases, mostly by computed tomography; and 7) color plates of the typical surgical highlights taken through the operating microscope.

The ten chapters include 1) subtotal petrosectomy, consisting of closing the eustachian tube and exenterating all pneumatic spaces of the temporal bone; 2) the transotic approach to the cerebellopontine angle, recommended by the authors mainly for removal of acoustic neuroma smaller than 2.5 cm; 3-5) infratemporal fossa approaches types A, B, and C, which provide access to the jugular foramen and along the intratemporal course of the internal carotid artery (A), to the petrous apex and clivus (B), and to the pterygopalatine fossa and nasopharynx (C); 6) the transtemporal supralabyrinthine approach, better known as the middle fossa approach; 7) the translabyrinthine approach, used by the authors only for cochleovestibular neurectomy; and 8) petrosectomy and radical dissection of the retromandibular fossa, mainly for malignant parotid tumors.

In contrast to all other otoneurosurgeons (House, Glasscock, Sterkers, Zini, and others, including myself) who have documented excellent results on large series in removal of acoustic neuromas larger than 2.5 cm by the translabyrinthine approach, Fisch and Mattox recommend the transotic approach for tumors smaller than 2.5 cm and the suboccipital approach for tumors larger than 2.5 cm. In this respect I cannot agree with the authors.

This is a superb atlas with much totally new information on the relatively new field of skull base surgery. Every otosurgeon who is performing any kind of surgery on the facial or eighth nerve, acoustic neuromas, or glomus tumors or other skull base surgery will benefit from this book. It should be in the library of every ENT department.

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May 19, 1989

Dr. Morton Cooper
10921 Wilshire Blvd. #401
Los Angeles, CA 90024

Dear Dr. Cooper:

How nice to hear from you in recent days! As you noted, my voice continues to hold strong. I have not had any problems with it since returning home in July of 1986.

I'm glad to hear that you are attempting to get word out about your needed therapy through various publishers and organizations. I give permission to use any portion of my thoughts here if they might help others afflicted with a serious voice problem find the help you are able to give.

I am grateful that your book, *"Change Your Voice, Change Your Life,"* was available to the general public back in 1986! I had struggled with "spastic dysphonia" for nine years, trying every voice therapist in our area, without improvement.

I tried bio-feedback, counseling (since some doctors thought it psychological), and more, without success. In March, 1986, I traveled to the famed Mayo Clinic, in Rochester, Minn. Little hope was given there, except the possibility of surgery to sever the nerve to one vocal cord, paralyzing it forever! But, I was told, this may not help. I opted not to do it!

Then, a parishioner gave me your book! After reading it, I wrote you and you contacted me about the possibility of direct therapy. The rest you know!

As I consider your work, I see it as a ministry, providing help, hope and wholeness for people who have reached the point of giving up on ever communicating normally again. Your therapy is simple but effective as you teach us to use our voice the way God intended it to be.

And as your techniques work wonders, there's a feeling of re-birth, not just for the voice but for the whole person! When you've come to believe you've lost something forever . . . and then receive it back again, it's like a miracle! I can't describe the joy! And it has brought a new vitality to my ministry. It's been a source of inspiration for my people as they see hope for themselves as they deal with problems that once seemed hopeless.

Through your therapy, you restore to those of us who had "spastic dysphonia" or other serious voice disorders the opportunity to experience again the very gift God has given us that makes us human: the gift of communication!

Blessings & thanks,

Jim

Pastor James M. Johnson

Let's Hear Your Views!

Please send your comments on spastic dysphonia to MORTON COOPER, Ph.D., Suite 401, 10921 Wilshire Blvd., Los Angeles, CA 90024.

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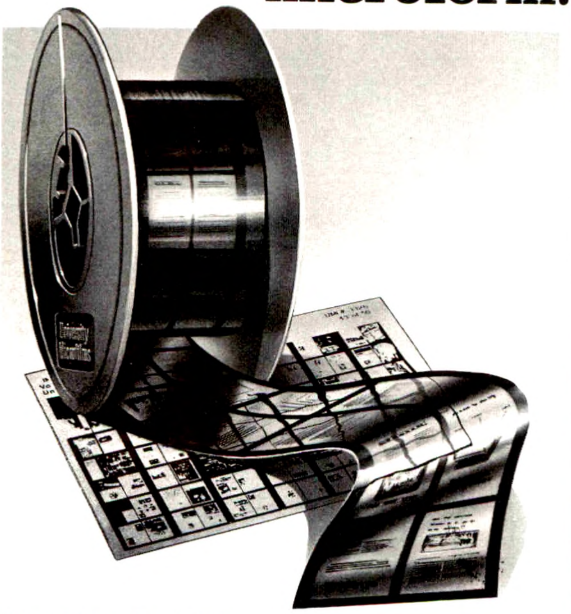

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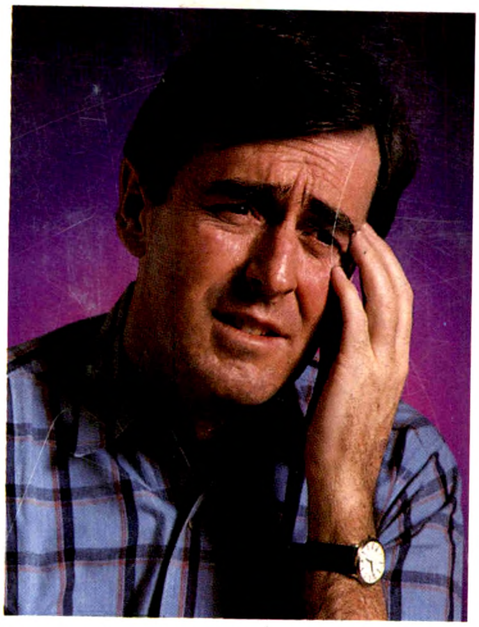

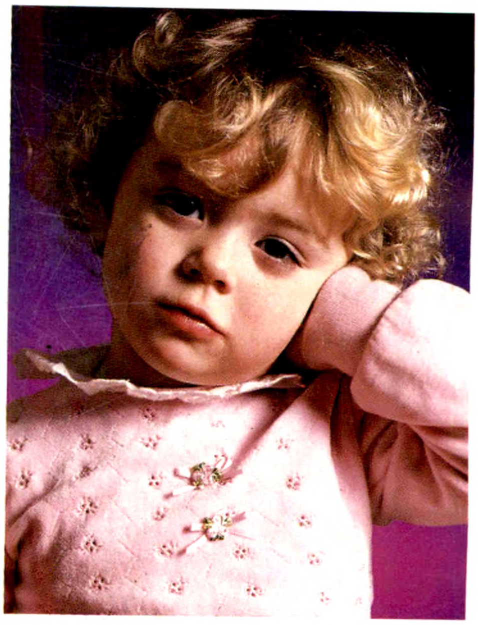

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